Panic Disorder

Diagnostic Criteria (F41.0)

A. Recurrent unexpected panic attacks. A panic attack is an abrupt surge of intense fear or intense discomfort that reaches a peak within minutes, and during which time four (or more) of the following symptoms occur:

Note: The abrupt surge can occur from a calm state or an anxious state.

1.

1. Palpitations, pounding heart, or accelerated heart rate.
2. Sweating.
3. Trembling or shaking.
4. Sensations of shortness of breath or smothering.
5. Feelings of choking.
6. Chest pain or discomfort.
7. Nausea or abdominal distress.
8. Feeling dizzy, unsteady, light-headed, or faint.
9. Chills or heat sensations.
10. Paresthesias (numbness or tingling sensations).
11. Derealization (feelings of unreality) or depersonalization (being detached from oneself).
12. Fear of losing control or “going crazy.”
13. Fear of dying.

Note: Culture-specific symptoms (e.g., tinnitus, neck soreness, headache, uncontrollable screaming or crying) may be seen. Such symptoms should not count as one of the four required symptoms.

B. At least one of the attacks has been followed by 1 month (or more) of one or both of the following:

1. Persistent concern or worry about additional panic attacks or their consequences (e.g., losing control, having a heart attack, “going crazy”).
2. A significant maladaptive change in behavior related to the attacks (e.g., 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 (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism, cardiopulmonary disorders).

D. The disturbance is not better explained by another mental disorder (e.g., the panic attacks do not occur only in response to feared social situations, as in social anxiety disorder; in response to circumscribed phobic objects or situations, as in specific phobia; in response to obsessions, as in obsessive-compulsive disorder; in response to reminders of traumatic events, as in posttraumatic stress disorder; or in response to separation from attachment figures, as in separation anxiety disorder).

Diagnostic Features

Panic disorder is characterized by recurrent unexpected panic attacks (Criterion A). (For a detailed description of symptoms and course characterizing a panic attack, see Panic Attack Specifier, "Features" section, following this text on panic disorder.) A *panic attack* is an abrupt surge of intense fear or intense discomfort that reaches a peak within minutes, and during which time 4 or more of a list of 13 physical and cognitive symptoms occur. The term *recurrent* means more than one unexpected panic attack. The term *unexpected* refers to a panic attack for which there is no obvious cue or trigger at the time of occurrence—that is, the attack appears to occur from out of the blue, such as when the individual is relaxing or emerging from sleep (nocturnal panic attack). In contrast, *expected* panic attacks are those for which there is an obvious cue or trigger, such as a situation in which panic attacks have typically occurred. The determination of whether panic attacks are expected or unexpected is made by the clinician, who makes this judgment based on a combination of careful questioning as to the sequence of events preceding or leading up to the attack and the individual's own judgment of whether the attack seemed to occur for no apparent reason. Cultural interpretations may influence the assignment of panic attacks as expected or unexpected (see section "Culture-Related Diagnostic Issues" for this disorder). In the United States and Europe, approximately one-half of individuals with panic disorder have expected panic attacks as well as unexpected panic attacks (Craske et al. 2010). Thus, the presence of expected panic attacks does not rule out the diagnosis of panic disorder.

The frequency and severity of panic attacks vary widely. In terms of frequency, there may be moderately frequent attacks (e.g., one per week) for months at a time, or short bursts of more frequent attacks (e.g., daily) separated by weeks or months without any attacks or with less frequent attacks (e.g., two per month) over many years. Individuals who have infrequent panic attacks resemble those with more frequent panic attacks in terms of panic attack symptoms, demographic characteristics, comorbidity with other disorders, family history, and biological data (Craske et al. 2010). In terms of severity, individuals with panic disorder may have both full-symptom (four or more symptoms) and limited-symptom (fewer than four symptoms) attacks, and the number and type of panic attack symptoms frequently differ from one panic attack to the next (Craske et al. 2010). However, more than one unexpected full-symptom panic attack is required for the diagnosis of panic disorder.

A *nocturnal* panic attack (i.e., waking from sleep in a state of panic) differs from panicking after fully waking from sleep. In the United States, nocturnal panic attack has been estimated to occur at least one time in roughly one-quarter to one-third of individuals

with panic disorder, of whom the majority also have daytime panic attacks (Craske and Rowe 1997). Individuals with both daytime and nocturnal panic attacks tend to have more severe panic disorder overall (Nakamura et al. 2014).

The worries about panic attacks or their consequences usually pertain to physical concerns, such as worry that panic attacks reflect the presence of life-threatening illnesses (e.g., cardiac disease, seizure disorder); social concerns, such as embarrassment or fear of being judged negatively by others because of visible panic symptoms; and concerns about mental functioning, such as "going crazy" or losing control (Criterion B). Individuals who report fears of dying in their panic attacks tend to have more severe presentations of panic disorder (e.g., panic attacks involving more symptoms) (Gazarian et al. 2016). The maladaptive changes in behavior represent attempts to minimize or avoid panic attacks or their consequences. Examples include avoiding physical exertion, reorganizing daily life to ensure that help is available in the event of a panic attack, restricting usual daily activities, and avoiding agoraphobia-type situations, such as leaving home, using public transportation, or shopping. If agoraphobia is present, a separate diagnosis of agoraphobia is given.

Associated Features

In addition to worry about panic attacks and their consequences, many individuals with panic disorder report constant or intermittent feelings of anxiety that are more broadly related to health and mental health concerns. For example, individuals with panic disorder often anticipate a catastrophic outcome from a mild physical symptom or medication side effect (e.g., thinking that they may have heart disease or that a headache means presence of a brain tumor). Such individuals often are relatively intolerant of medication side effects. In addition, there may be pervasive concerns about abilities to complete daily tasks or withstand daily stressors, excessive use of drugs (e.g., alcohol, prescribed medications or illicit drugs) to control panic attacks, or extreme behaviors aimed at controlling panic attacks (e.g., severe restrictions on food intake or avoidance of specific foods or medications because of concerns about physical symptoms that provoke panic attacks).

Prevalence

In the general population, the 12-month prevalence estimate for panic disorder across the United States and several European countries is about 2%–3% in adults and adolescents (Goodwin et al. 2005; Kessler et al. 2012; Olaya et al. 2018). The global lifetime prevalence is estimated at 1.7%, with a 2.7% projected lifetime risk in the World Mental Health Surveys (de Jonge et al. 2016). In the United States, significantly lower prevalence estimates of panic disorder are reported among Latinx, African Americans, Caribbean Blacks, and Asian Americans, compared with non-Latinx Whites (Levine et al. 2013; Lewis-Fernández et al. 2010). Prevalence estimates of panic disorder in American Indians range from 2.6% to 4.1% (Sawchuk et al. 2017). Lower estimates have been reported for Asian, African, and Latin American countries, ranging from 0.1% to 0.8% (Lewis-Fernández et al. 2010; Wong et al. 2016). Women are more frequently affected than men, at a rate of approximately 2:1 (de Jonge et al. 2016; McLean et al. 2011; Moreno-Peral et al. 2014). The gender differentiation occurs in adolescence and is already observable before age 14 years (Nelemans et al. 2014). Although panic attacks occur in children, the overall prevalence of panic disorder is low before age 14 years (<0.4%) (Craske et al. 2010). The rates of panic disorder show a gradual increase during adolescence and possibly following the onset of puberty, and peak during adulthood (Merikangas et al. 2010). The prevalence declines in older individuals (i.e., 1.2%

in adults older than age 55, 0.7% in adults older than age 64) (Chou 2010; Kessler et al. 2012), possibly reflecting diminishing severity to subclinical levels (Mohlman et al. 2012; Wolitzky-Taylor et al. 2010).

Development and Course

The median age at onset for panic disorder in the United States is 20–24 years (Kessler et al. 2005), and cross-nationally is 32 years (de Jonge et al. 2016). The mean age at onset is 34.7 years (Berenz et al. 2019). A small number of cases begin in childhood, and onset after age 55 years is unusual but can occur (Chou 2010). The usual course, if the disorder is untreated, is chronic but waxing and waning (Nay et al. 2013; Scholten et al. 2013). Some individuals may have episodic outbreaks with years of remission in between, and others may have continuous severe symptomatology. According to a longitudinal study in the Netherlands, about one-quarter of the individuals with panic disorder experienced recurrence of symptoms within the initial 2-year follow-up period (Scholten et al. 2013). Only a minority of individuals have full remission without subsequent relapse within a few years (Nay et al. 2013). The course of panic disorder typically is complicated by a range of other disorders, in particular other anxiety disorders, depressive disorders, and substance use disorders (see section "Comorbidity" for this disorder). African American adults have been reported to have a more chronic course of panic disorder compared with non-Latinx White adults, possibly because of the enduring impact of racism and discrimination, stigma due to mental illness, and limited access to adequate care (Hunter and Schmidt 2010; Sibrava et al. 2013).

Although panic disorder is very rare in childhood, first occurrence of "fearful spells" is often dated retrospectively back to childhood (Pine and Klein 2008). As in adults, panic disorder in adolescents tends to have a chronic course and is frequently comorbid with other anxiety, depressive, and bipolar disorders. To date, no differences in the clinical presentation between adolescents and adults have been found. However, adolescents may be less worried about additional panic attacks than are young adults (Craske et al. 2010). Lower prevalence of panic disorder in older adults appears to be attributable to age-related "dampening" of the autonomic nervous system response (Mohlman et al. 2012). Many older individuals with "panicky feelings" are observed to have a "hybrid" of limited-symptom panic attacks and generalized anxiety. Also, older adults tend to attribute their panic attacks to certain stressful situations, such as a medical procedure or social setting. Older individuals may retrospectively endorse explanations for the panic attack (which would preclude the diagnosis of panic disorder), even if an attack might actually have been unexpected in the moment (and thus qualify as the basis for a panic disorder diagnosis). This may result in under-endorsement of unexpected panic attacks in older individuals. Thus, careful questioning of older adults is required to assess whether panic attacks were expected before entering the situation, so that unexpected panic attacks and the diagnosis of panic disorder are not overlooked.

While the low rate of panic disorder in children could relate to difficulties in symptom reporting, this seems unlikely given that children are capable of reporting intense fear or panic in relation to separation and to phobic objects or phobic situations. Adolescents might be less willing than adults to openly discuss panic attacks. Therefore, clinicians should be aware that unexpected panic attacks do occur in adolescents, much as they do in adults, and be attuned to this possibility when encountering adolescents presenting with episodes of intense fear or distress.

Risk and Prognostic Factors

Temperamental

Negative affectivity (neuroticism) (i.e., proneness to experiencing negative emotions), anxiety sensitivity (i.e., the disposition to believe that symptoms of anxiety are harmful), behavioral inhibition, and harm avoidance are risk factors for the onset of panic attacks and panic disorder (Asselmann et al. 2016; McNally 2002; Naragon-Gainey 2010; Roy-Byrne et al. 2006). History of "fearful spells" (i.e., limited-symptom attacks that do not meet full criteria for a panic attack) may be a risk factor for later panic attacks and panic disorder, particularly when the first panic experience is appraised as negative (Asselmann et al. 2014). Although separation anxiety in childhood, especially when severe, may precede the later development of panic disorder, it is not a consistent risk factor (Craske et al. 2010).

Environmental

Most individuals report identifiable stressors in the months before their first panic attack (e.g., interpersonal stressors and stressors related to physical well-being, such as negative experiences with illicit or prescription drugs, disease, or death in the family). Furthermore, more chronic life stress is associated with greater panic disorder severity (Conway et al. 2016). Between 10% and 60% of individuals with panic disorder endorse a history of trauma (Fernandes and Osório 2015), and stressful life experiences and childhood adversities are associated with more severe panic pathology (Asselmann et al. 2018). Parental overprotection and low emotional warmth are also risk factors for panic disorder (Asselmann et al. 2016). Individuals with few economic resources are more likely to have symptoms that meet criteria for panic disorder (Moreno-Peral et al. 2014). Smoking is a risk factor for panic attacks and panic disorder (Isensee et al. 2003; Moreno-Peral et al. 2014).

Genetic and physiological

Multiple genes likely confer vulnerability to panic disorder; however, the exact genes, gene products, or functions related to the genetic regions implicated remain unknown (Johnson et al. 2014). There is an increased risk for panic disorder among offspring of parents with anxiety, depressive, and bipolar disorders (Moreno-Peral et al. 2014).

Individuals with panic disorder display particularly enhanced sensitivity to respiratory stimulation using CO2-enriched air (Battaglia et al. 2009; Roberson-Nay et al. 2010). Respiratory disturbance, such as asthma, may be associated with panic disorder, in terms of past history, comorbidity, and family history (Kircanski et al. 2009).

Culture-Related Diagnostic Issues

The rate of fears about mental and somatic symptoms of anxiety appears to vary across cultural contexts and may influence the rate of panic attacks and panic disorder (Lewis-Fernández et al. 2010). Also, cultural expectations may influence the classification of panic attacks as expected or unexpected. For example, a Vietnamese individual who has a panic attack after walking out into a windy environment (*trúng gió;* "hit by the wind") may attribute the panic attack to exposure to wind as a result of the cultural syndrome that links these two experiences, resulting in classification of the panic attack as expected (Hinton et al. 2003). Various other cultural concepts of distress are associated with panic disorder, including *ataque de nervios* ("attack of nerves") among Latin Americans and *khyâl* attacks and "soul loss" among Cambodians (Lewis-Fernández et al. 2010). *Ataque de nervios* may involve trembling, uncontrollable screaming or crying,

aggressive or suicidal behavior, and depersonalization or derealization, which may be experienced longer than the few minutes typical of panic attacks (Lewis-Fernández et al. 2010). Some clinical presentations of *ataque de nervios* fulfill criteria for conditions other than panic attack (e.g., functional neurological symptom disorder). These concepts of distress have an impact on the symptoms and frequency of panic disorder, including the individual's attribution of unexpectedness, as cultural concepts of distress may create fear of certain situations, ranging from interpersonal arguments (associated with *ataque de nervios*), to types of exertion (associated with *khyâl* attacks), to atmospheric wind (associated with *trúng gió* attacks). Clarification of the details of cultural attributions may aid in distinguishing expected and unexpected panic attacks (Craske et al. 2010). For more information regarding cultural concepts of distress, refer to the "Culture and Psychiatric Diagnosis" chapter in Section III.

The specific worries about panic attacks or their consequences are likely to vary across ethnoracial groups and cultural contexts (and across different age groups and gender). Among Asian Americans, Hispanic Americans, and African Americans in the United States, panic disorder is associated with reports of ethnic discrimination and racism, after the effect of demographic factors is taken into account (Chou et al. 2012). For panic disorder, U.S. community samples of non-Latinx Whites have significantly less functional impairment than African Americans (Lewis-Fernández et al. 2010). There are also higher rates of objectively defined severity in non-Latinx Caribbean Blacks with panic disorder, and lower reported rates of panic disorder overall in both African Americans and Caribbean Blacks, suggesting that among U.S. community samples of African descent, panic disorder criteria may be endorsed only when there is substantial severity and impairment. The rate of mental health service use for panic disorder varies across ethnoracial groups (Levine et al. 2013).

Sex- and Gender-Related Diagnostic Issues

The rate of panic disorder is nearly twofold higher in women compared with men (de Jonge et al. 2016). Relapse from panic disorder also occurs more frequently in adult women compared with men, suggesting that women have a more unstable illness course (Yonkers et al. 2003). Gender differences in clinical course are also found among adolescents (Ohannessian et al. 2017). Panic disorder has a larger impact on health-related quality of life in women than in men (Kim et al. 2017), which may be attributable to greater anxiety sensitivity among some women or greater comorbidity with agoraphobia and depression. There is some evidence for sexual dimorphism, with high expression of *MAOA*-uVNTR alleles potentially acting as a female-specific risk factor for panic disorder (Reif et al. 2012).

Diagnostic Markers

Individuals with panic disorder exhibit an attentional bias to threatening stimuli (Pergamin-Hight et al. 2015). Panic attacks may be provoked by agents with disparate mechanisms of action, such as sodium lactate, caffeine, isoproterenol, yohimbine, CO_2, and cholecystokinin, to a much greater extent in individuals with panic disorder than in those without it (Roy-Byrne et al. 2006). There is considerable interest in the relationship between panic disorder and sensitivity to these panic-provoking agents. While none of the data suggest diagnostic utility, data for sensitivity to respiratory stimulation reflect some level of specificity for panic disorder and related conditions, such as separation anxiety disorder. Chronically higher baseline hyperventilation and rate of sighing may occur among individuals with panic disorder (Grassi et al. 2013). However, none of these laboratory findings are considered diagnostic of panic disorder.

Association With Suicidal Thoughts or Behavior

Panic attacks and a diagnosis of panic disorder in the past 12 months are related to a higher rate of suicidal behavior and suicidal thoughts in the past 12 months even when comorbidity and a history of childhood abuse and other suicide risk factors are taken into account (Roy-Byrne et al. 2006). Approximately 25% of primary care patients with panic disorder report suicidal thoughts (Teismann et al. 2018). Panic disorder may increase risk for future suicidal behaviors but not deaths (Bentley et al. 2016).

Epidemiological survey data of panic attack symptoms show that the cognitive symptoms of panic (e.g., derealization) may be associated with suicidal thoughts, whereas physical symptoms (e.g., dizziness, nausea) may be associated with suicidal behaviors (Rappaport et al. 2014).

Functional Consequences of Panic Disorder

Panic disorder is associated with high levels of social, occupational, and physical disability; considerable economic costs; and the highest number of medical visits among the anxiety disorders, although the effects are strongest with the presence of agoraphobia (Alonso et al. 2018; Wittchen et al. 2010). Individuals with panic disorder may be frequently absent from work or school for doctor and emergency room visits, which can lead to unemployment or dropping out of school (Alonso et al. 2019). In older adults, impairment may be seen in caregiving duties or volunteer activities, and panic disorder is related to lower health-related quality of life and greater receipt of emergency department services (Chou 2010). Full-symptom panic attacks typically are associated with greater morbidity (e.g., greater health care utilization, more disability, poorer quality of life) than limited-symptom attacks (Craske et al. 2010).

Differential Diagnosis

Only limited-symptom panic attacks

Panic disorder should not be diagnosed if full-symptom (unexpected) panic attacks have never been experienced. In the case of only limited-symptom unexpected panic attacks, an other specified anxiety disorder or unspecified anxiety disorder diagnosis should be considered.

Anxiety disorder due to another medical condition

Panic disorder is not diagnosed if the panic attacks are judged to be a direct physiological consequence of another medical condition. Examples of medical conditions that can cause panic attacks include hyperthyroidism, hyperparathyroidism, pheochromocytoma, vestibular dysfunctions, seizure disorders, and cardiopulmonary conditions (e.g., arrhythmias, supraventricular tachycardia, asthma, chronic obstructive pulmonary disease [COPD]) (Fava et al. 2010; Johnson et al. 2018; Meuret et al. 2017; Moreno-Peral et al. 2014; Ohayon 2014). Appropriate laboratory tests (e.g., serum calcium levels for hyperparathyroidism; Holter monitor for arrhythmias) or physical examinations (e.g., for cardiac conditions) may be helpful in determining the etiological role of another medical condition. Features such as onset after age 45 years or the presence of atypical symptoms during a panic attack (e.g., vertigo, loss of consciousness, loss of bladder or bowel control, slurred speech, amnesia) suggest the possibility that another medical condition or a substance may be causing the panic attack symptoms.

Substance/medication-induced anxiety disorder

Panic disorder is not diagnosed if the panic attacks are judged to be a direct physiological consequence of a substance. Intoxication with central nervous system stimulants (e.g., cocaine, amphetamine-type substances, caffeine) or cannabis and withdrawal from central nervous system depressants (e.g., alcohol, barbiturates) can precipitate a panic attack (Alvarado et al. 2010; Ross et al. 2012).

However, if panic attacks continue to occur outside of the context of substance use (e.g., long after the effects of intoxication or withdrawal have ended), a diagnosis of panic disorder should be considered. In addition, because panic disorder may precede substance use in some individuals and may be associated with increased substance use, especially for purposes of self-medication, a detailed history should be taken to determine if the individual had panic attacks prior to excessive substance use. If this is the case, a diagnosis of panic disorder should be considered in addition to a diagnosis of substance use disorder. Features such as onset after age 45 years or the presence of atypical symptoms during a panic attack (e.g., vertigo, loss of consciousness, loss of bladder or bowel control, slurred speech, amnesia) suggest the possibility that another medical condition or a substance may be causing the panic attack symptoms.

Other mental disorders with panic attacks as an associated feature (e.g., other anxiety disorders and psychotic disorders)

Panic attacks that occur as a symptom of other anxiety disorders are expected (e.g., triggered by social situations in social anxiety disorder, by phobic objects or situations in specific phobia or agoraphobia, by worry in generalized anxiety disorder, by separation from home or attachment figures in separation anxiety disorder) and thus would not meet criteria for panic disorder. (**Note:** Sometimes an unexpected panic attack is associated with the onset of another anxiety disorder, but then the attacks become expected, whereas panic disorder is characterized by recurrent unexpected panic attacks.) If the panic attacks occur only in response to specific triggers, then only the relevant anxiety disorder is assigned. However, if the individual experiences unexpected panic attacks as well and shows persistent concern and worry or behavioral change because of the attacks, then an additional diagnosis of panic disorder should be considered.

Comorbidity

Panic disorder infrequently occurs in clinical settings in the absence of other psychopathology. In the general population, 80% of individuals with panic disorder had a lifetime comorbid mental diagnosis (de Jonge et al. 2016). The prevalence of panic disorder is elevated in individuals with other disorders, particularly other anxiety disorders (and especially agoraphobia), major depressive disorder, bipolar I and bipolar II disorder, and possibly mild alcohol use disorder (Kessler et al. 2005). While panic disorder occasionally has an earlier age at onset than the comorbid disorder(s), onset often occurs after the comorbid disorder (e.g., de Jonge et al. 2016; Goodwin and Stein 2013) and may be seen as a severity marker of the comorbid illness.

Reported lifetime rates of comorbidity between major depressive disorder and panic disorder vary widely, ranging from 10% to 65% in individuals with panic disorder (Roy-Byrne et al. 2000). In approximately one-third of individuals with both disorders, the depression precedes the onset of panic disorder. In the remaining two-thirds, depression occurs coincident with or following the onset of panic disorder. A subset of individuals with panic disorder develop a substance-related disorder, which for some represents an

attempt to treat their anxiety with alcohol or medications (Zimmermann et al. 2003). Comorbidity with other anxiety disorders and illness anxiety disorder is also common.

Panic disorder is significantly comorbid with numerous general medical symptoms and conditions, including, but not limited to, dizziness, cardiac arrhythmias, hyperthyroidism, asthma, COPD, and irritable bowel syndrome (Grzesiak et al. 2014; Livermore et al. 2010). However, the nature of the association (e.g., cause and effect) between panic disorder and these conditions remains unclear. Although mitral valve prolapse and thyroid disease are more common among individuals with panic disorder than in the general population, the increases in prevalence are not consistent.

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