CHAPTER 4

PANIC DISORDER

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The purpose of this chapter is to offer an up-to-date review on the nature, etiology, assessment, and treatment of panic disorder. The chapter aims to integrate a substantial body of previous research on panic disorder with the most recent advances in the field.

Description of Panic Disorder

Description of Symptoms and Criteria

A panic attack is an abrupt surge of intense fear or discomfort that is diagnostically characterized by a cluster of 13 physical and cognitive symptoms, including palpitations, shortness of breath, parasthesias, trembling, derealization, and fears of dying, going crazy, or losing control (American Psychiatric Association [APA], 1994). The panic attack is discrete, having a sudden, abrupt onset and relatively brief duration (with symptoms peaking within 10 minutes of onset), as opposed to gradually building anxious arousal. A *full-blown* panic attack is defined as four or more symptoms, whereas *limited symptom* attacks are defined as fewer than four symptoms.

Panic attacks are characterized by a unique action tendency: Specifically, urges to escape, and less often, urges to fight. In other words, panic attacks represent activation of the fight-flight system. Accordingly, panic attacks usually involve elevated autonomic nervous system arousal, needed to support such fight-flight reactivity. Furthermore, perceptions of imminent threat, such as death, loss of control, or social ridicule frequently accompany the fight-flight responsee. However, the urgency to escape, autonomic arousal, and perception of threat are not present in every self-reported occurrence of panic. For example, data gathered from ambulatory (portable) devices have found sympathetic nervous system activation (Wilkinson et al., 1998) although nonactivation has also been documented (for ~40% of self-reported panic attacks, see Margraf, Taylor, Ehlers, Roth, & Agras, 1987; Taylor, Sheikh, Agras, Roth, Margraf, Ehlers, Maddock, & Gossard, 1986). Severe panic attacks are more autonomically based (Margraf et al., 1987). Self-reported panic in the absence of actual autonomic activation is assumed to reflect anticipatory anxiety versus true panic (Barlow, Brown, & Craske, 1994). Another discordant example occurs when perceptions of threat or danger are refuted, despite the report of intense fear and arousal. This has been termed *noncognitive* panic (Rachman, Lopatka, & Levitt, 1988).

Panic attacks may be experienced by individuals diagnosed with any of the anxiety disorders, and they are common in all of these disorders. Panic disorder is distinguished by unexpected panic attacks, or attacks that occur without an obvious trigger, and at least 1 month of persistent apprehension about the recurrence of panic or its consequences, or a significant behavioral change. These behavioral changes may include safety behaviors, such as frequent attendance at medical facilities for fear of a medical problem, or agoraphobia. Agoraphobia refers to avoidance, or endurance with dread, of situations from which escape might be difficult or in which help might be unavailable in the event of a panic attack, or paniclike symptoms, such as loss of bowel control. Typical agoraphobic situations include shopping malls, waiting in line, movie theaters, traveling by car or bus, crowded restaurants and stores, and being alone.

A subset of individuals who have panic disorder also experience *nocturnal* panic attacks. Nocturnal panic refers to waking from sleep in a state of panic with symptoms that are very similar to panic attacks that occur during wakeful states (Uhde, 1994; Craske & Barlow, 1989). Nocturnal panic does *not* refer to waking from sleep and panicking after a lapse of waking time, or night-time arousals induced by nightmares or environmental stimuli (such as unexpected noises). Also, nocturnal panic is distinct from sleep terrors and sleep apnea (see Craske & Tsao, 2005, for a review).

Although epidemiological studies have not been conducted, surveys of select clinical groups suggest that nocturnal panic is relatively common among individuals with panic disorder, with 44% to 71% reporting nocturnal panic at least once, and 30% to 45% reporting repeated nocturnal panics (Craske & Barlow, 1989; Krystal, Woods, Hill, & Charney, 1991; Mellman & Uhde, 1989<AQ: Reference entry needed>; Roy-Byrne, Mellman, & Uhde, 1988; Uhde, 1994). Individuals who suffer frequent nocturnal panics often become fearful of sleep and attempt to delay sleep onset. Avoidance of sleep may result in chronic sleep deprivation, in turn precipitating more nocturnal panics (Uhde).

Case Example

Sandy is a 30-year-old Caucasian mother of a 5 year old and a 3 year old, who lives with her husband of 6 years. For the past 2 years, she has been chronically anxious and panic stricken. Her panic attacks are described as intolerable and increasing in frequency. The first time that she panicked was 3 years ago, just after the birth of her second child. She recalls suddenly experiencing strong sensations of lightheadedness and weakness when she was at home with her newborn and 2 –year-old children. She was convinced that she was about to pass out. She immediately laid down. The feelings passed within a few minutes, but Sandy remained very concerned that she would pass out. This

concern was particularly worrisome since Sandy feared what would happen to her children if she lost consciousness. She felt anxious for a day or so but then forgot about the feelings until a few weeks later, when again, at home alone with her children, she was overcome with even stronger sensations of lightheadedness, weakness, and a cold sweat. She became very afraid, especially for her children, and called her husband, who left work to be with her. A visit to her primary care doctor the next day did not reveal any medical explanations for the symptoms. Nonetheless, Sandy began to pay close attention to her physical state and became very anxious about her husband's upcoming business trip. While her husband was away, she panicked daily, each time phoning her mother, who would come over to look after the children while Sandy laid down until the feelings subsided. From that time onward, Sandy was very anxious about being alone with her children.

Now Sandy has these feelings in many situations. She describes her panic attacks as intense feelings of lightheadedness, weakness, a sense of unreality and detachment, a racing heart, nausea, and fears of losing consciousness. It is the lightheadedness and unreality that scare her the most, for fear of passing out and leaving her children unattended. Consequently, Sandy is now sensitive to anything that produces lightheaded and unreal types of feelings, such as standing quickly from a seated position, heat, the semiconsciousness that occurs just before falling asleep, bright lights, alcohol, and drugs. Even though she has a prescription for Klonopin (a high-potency benzodiazepine), she rarely uses medication because of her fear of feeling "weird" and unable to take care of her children. She wants to be as alert as possible at all times, but she keeps the Klonopin with her in the event that she has no other escape route. She is very sensitive to her body in general—she becomes scared of anything that feels a little different than usual. Even coffee, which she used to enjoy, is distressing to her now because of its agitating and racy effects. She was never a big exerciser, but to think of exerting herself now is also scary. She reports that she is constantly waiting for the next panic to occur. She avoids being alone with her children and situations where she thinks she is more likely to pass out, such as driving, restaurants, and long distances from home. She avoids crowds and large groups as well, partly because of the feeling of too much stimulation and partly because she is afraid she might panic in front of others. Also, Sandy avoids unstructured time, in the event she might dwell on how she feels and, by so doing, panic. She tries to keep herself as busy as possible with her children but remains constantly anxious about the possibility of panicking and passing out. In general, she prefers to be with her husband or her mother.

In fact, her reliance on her husband and mother has strained those relationships. Her husband is frustrated with Sandy's behavior and the restrictions it has placed on his own life: he no longer goes on business trips, he spends every free moment with Sandy and the children, and sometimes he has to leave work to come home because Sandy's mother is not available to be with her. Similarly,

while her mother offers to help as much as possible, she is also feeling that Sandy's reliance upon her is too much.

Sandy describes how different she is from the way she used to be: how weak and scared she is now. The only other incident that has any similarity to her current panic attacks occurred in her late teens when she smoked marijuana. Sandy recalls being very scared of the feeling of losing control and the sense that she would never return to reality. She has not taken drugs since then. Otherwise she has no history of serious medical conditions or any previous psychological treatment. Sandy was shy as a young child and throughout her teens. However, her social anxiety improved throughout her 20s to the point that, up until the onset of her panic attacks, she was mostly very comfortable around people. Since the onset of her panic attacks, she has become concerned that others will notice that she appears different or strange. However, her social anxiety is limited to panic attacks and does not reflect a broader social phobia.

In general, her appetite is good but her sleep is restless. At least once a week she wakes abruptly in the middle of the night with a panic attack, feeling short of breath and scared. Sandy is mostly worried about her panic attacks. She worries about what will happen to her children if she loses consciousness, but she also worries what will happen to them in the long term, if she continues to panic. She has some difficulty concentrating, but in general she functions well when she feels safe—that is, when her mother or husband are nearby. She sometimes becomes depressed about her panic and the limitations on her independence. She occasionally has times of feeling hopeless about the future, doubting if she will ever be able to get back to feeling like she did before these attacks began.

Brief History

Panic disorder was first regarded as a diagnostic entity with the publication of the *DSM III,* 25 years ago. Prior to that time, panic attacks were viewed as symptoms of a general neurosis, although accounts of a clinically similar syndrome appeared much earlier. These were labeled as *soldiers heart* (Wooley, 1982), *neurocirculatory asthenia* (Wheeler, White, Reed, & Cohen, 1950), and *effort syndrome* (Nixon, 1993). In the *DSM-III,* agoraphobia was considered a separate disorder, which might or might not be associated with panic attacks. Observations of clinical samples by Klein (1981) and others (Craske & Barlow, 1988; Turner, Williams, Beidel, & Mezzich, 1986) suggested that agoraphobia generally developed following panic attacks, and this led to a redefinition of agoraphobia as a secondary response to panic attacks in the *DSM-III-R* (Barlow, 2002). However, the debate continues (see the epidemiology section), and the latest *DSM* (*DSM-IV-TR* [American Psychiatric Association], 1994) retains agoraphobia without a history of Panic Disorder as a separate diagnosis.

In contrast to earlier *DSM* diagnostic criteria, greater recognition is given in *DSM-IV* to the notion that panic attacks may occur in the context of any anxiety disorder. Panic attacks are categorized as either situationally bound, situationally predisposed, or unexpected/uncued. Panic Disorder is diagnosed when there are repeated unexpected/uncued panic attacks and persistent apprehension about panic attacks and/or behavioral changes resultant from panic attacks.

Epidemiology

From the National Comorbidity Survey-Replication (NCS-R), prevalence estimates for Panic Disorder are 2.7% (12 month) and 4.7% (lifetime; Kessler, Berglund, Demler, Jin, Merikangas, & Walters, 2005a; Kessler, Chiu, Demler, Merikangas, & Walters, 2005b). These rates are higher than those reported in the original NCS (Kessler et al. 1994) and the older Epidemiological Catchment Area (ECA) study (Myers et al. 1984). In addition, they are higher than recent estimates from the Ukraine (Bromet et al., 2005), Japan (Kawakami et al., 2005) and Germany (Goodwin, Fergusson, & Horwood, 2005). While data from the United States suggests increased prevalence over the past two decades (Goodwin 2003), the data from other countries raises the possibility that the range in prevalence rates reflects differences in diagnostic methodology as well as variations in diagnostic criteria.

In contrast to individuals with agoraphobia who seek treatment, who almost always report a history of panic that preceded development of their avoidance (Wittchen, Reed, & Kessler, 1998), epidemiological data indicate relatively high rates for agoraphobia without a history of panic disorder: 0.8% in the last 12 months (versus 2.8% for Panic Disorder; Kessler et al., 2005a) and 1.4% lifetime prevalence (versus 4.7% for Panic Disorder: Kessler et al., 2005b). These rates are considerably lower than previous epidemiological estimates by Kessler and colleagues (1994) of 2.8% for agoraphobia without panic in the last 12 months and 5.3% over the lifetime. The more recent data still indicate that the rate of agoraphobia without a history of Panic Disorder occurs at nearly one third the rate of Panic Disorder. The earlier epidemiological data may have overestimated agoraphobia prevalence due to misdiagnosis of Generalized Anxiety, specific and social phobias, and reasonable cautiousness about certain situations (e.g., walking alone in unsafe neighborhoods) as agoraphobia (Horwath, Lish, Johnson, Hornig, & Weissman, 1993). The more general discrepancy between the clinical and epidemiology data may occur because individuals who panic are more likely to seek help (Boyd, 1986).

Rarely does the diagnosis of Panic Disorder, with or without agoraphobia, occur in isolation. Commonly co-occurring Axis I conditions include specific phobias: Social Phobia, Dysthymia, Generalized Anxiety Disorder, Major

Depressive Disorder, and substance abuse (e.g., 60% [Brown, Campbell, Lehman, Gishman, & Mancill, 2001]; 51% [Brown, Antony, & Barlow, 1995]; 51% [Kessler, Chiu, Demler, Merikangas, & Walker, 2005b]) Also, from 25% to 60% of persons with Panic Disorder meet criteria for a current comorbid personality disorder, mostly avoidant or dependent personality disorders (e.g., Chambless & Renneberg, 1988).

The modal age of onset for Panic Disorder is early adulthood, between age 21 and 23, although there is significant variability in onset period (Kessler et al., 2006<AQ: Reference entry needed>). In fact, a substantial proportion of adolescents report panic attacks (e.g., Hayward et al., 1992). Panic Disorder in children and adolescents tends to be chronic and comorbid with other anxiety, mood, and disruptive disorders (Biederman et al., 1997). Treatment is usually sought at a much later age, around 34 years (e.g., Noyes, Crowe, Harris, Hamra, McChesney, & Chaudhry, 1986). The overall ratio of females to males is approximately 2:1 (Kessler et al., 2006) although the ratio shifts dramatically in the direction of female predominance as the level of agoraphobia worsens (e.g., Thyer, Himle, Curtis, Cameron, & Nesse, 1985).

Most individuals with Panic Disorder With or Without Agoraphobia (approximately 72%; Craske, Miller, Rotunda, & Barlow, 1990) report identifiable stressors around the time of their first panic attack. These include interpersonal stressors and stressors related to physical well-being, such as negative drug experiences, disease, or death in the family. However, the number of stressors does not differ from the number experienced prior to the onset of other types of anxiety disorders (Pollard, Pollard, & Corn, 1989; Rapee, Litwin, & Barlow, 1990; Roy-Byrne, Geraci, & Uhde, 1986). Approximately one half report having experienced panicky feelings at some time before their first full panic attack, suggesting that onset may be either insidious or acute (Craske et al., 1990).

Finally, Panic Disorder and agoraphobia tend to be chronic conditions, with severe financial and interpersonal costs. Individuals with Panic Ddisorder overutilize medical resources compared to the general public and to individuals with other psychiatric disorders (e.g., Roy-Byrne et al., 1999). Even with or following pharmacological treatment only a minority of patients remit without subsequent relapse (~30%), although a similar number experience notable improvement, albeit with a waxing and waning course (25–35%; Roy-Byrne & Cowley, 1995; Katschnig & Amering, 1998). Nevertheless, the prognosis for Panic Disorder, especially in the absence of agoraphobia, is more positive than for Generalized Anxiety Disorder or Social Anxiety Disorder (Bruce et al., 2005).

Actual Dysfunction

Neurobiology of Panic Disorder

Genetics

The trait of neuroticism confers risk for emotional disorders, including Panic Disorder (e.g., Mineka, Watson, & Clark, 1998). Numerous multivariate genetic analyses of human twin samples consistently attribute approximately 50% of the variance in neuroticism to additive genetic factors (Lake, Eaves, Maes, Heath, & Martin, 2000). In addition, anxiety and depression appear to be variable expressions of the heritable tendency toward neuroticism (Kendler, Heath, Martin, & Eaves, 1987). Twin studies provide evidence that symptoms of fear (i.e., breathlessness, heart pounding) may be additionally explained by a unique source of genetic variance that is differentiated from symptoms of depression and anxiety (Kendler et al.) and, at least in females, from neuroticism (Martin, Jardine, Andrews, & Heath, 1988).

Even though heritability studies of anxiety disorders rely on poorly validated lifetime diagnostic instruments (e.g., Diagnostic Interview Schedule), two broad but distinct genetic factors have been identified. The first is defined by high loadings for Generalized Anxiety Disorder and Major Depression, but only moderate loadings for Panic Disorder (Mineka, Watson, & Clark, 1998) and agoraphobia (Kendler, Neale, Kessler, Heath, & Eaves, 1993). The second is defined by high loadings for Panic Disorder (with and without agoraphobia) and phobias (Kendler et al., 1995). Support for these two broad diatheses exists in separate analyses of the Vietnam Era Twin Registry (Scherrer et al., 2000).

Analyses of specific genetic markers remain preliminary and inconsistent. For example, Panic Disorder has been linked to a locus on chromosome 13 (Hamilton et al., 2003; Schumacher et al., 2005<AQ: Reference entry needed>) and chromosome 9 (Gagunashvili et al., 2003<AQ: Reference entry needed>*)*, but the exact genes remain unknown. Findings regarding markers for the cholecystokinin-BE receptor gene have been inconsistent (van Megen, Westenberg, Den Boer, & Kahn, 1996 versus Hamilton et al., 2001). Association and linkage studies implicate the adenosine receptor gene in panic disorder (Deckert et al., 1998; Hamilton et al. 2004). However, studies of genes involved in neurotransmitter systems associated with fear and anxiety have produced inconsistent results (see Roy-Byrne, Stein & Craske, in press).

Basic Neurocircuitry

Amygdala. Current neural models focus on the role of the amgydala and related structures as central to the dysfunctional anxiety evaluation and response system in Panic Disorder (Gorman, Kent, Sullivan & Coplan, 2000). The amygdala serves as a mediator of input from the environment (via the thalamus and sensory cortex) and stored experience (via the frontal cortex and hippocampus), which then triggers the anxiety and panic response by activating brain regions involved in central panic symptoms, including the hypothalamus (HPA axis and autonomic system), locus ceruleus (heart rate and blood pressures), and parabrachial nucleus (changes in respiration; see Roy-Byrne, Stein & Craske, in press). Recent research on patients with Panic Disorder has found alterations in the amygdala and associated structures consistent with this model, including reduced volume in the amygdala (Massana et al., 2003) and left temporal lobe (Uchida et al., 2003), decreased cerebral glucose metabolism in amygdala, hippocampus, thalamus, and brain stem (Sakai et al., 2005), and lowered levels of creatine and phosphocreatine metabolites in the right medial temporal lobe (Massana et al., 2002). Many of these findings occur in various combinations in other anxiety disorders such as Social Anxiety and Posttraumatic Stress Disorder (Kent & Rauch, 2003), indicating that they are not necessarily specific to Panic Disorder.

GABA / Benzodiazepine System. Another neurological system potentially implicated in the pathophysiology of Panic Disorder is the γ-aminobutyric acid (GABA) neuronal system. Studies demonstrate that patients with Panic Disorder exhibit low baseline GABA levels in the occipital cortex (Goddard et al., 2001) and, following acute benzodiazepine administration, show blunted benzodiazepine sensitivity (Roy-Byrne, Cowley, Greenblatt, Shader & Hommer, 1990) and GABA neuronal responses (Goddard et al., 2004). Potentially elucidating these findings, several (Bremner et al., 2000; Malizia et al., 1998) but not all (Brandt et al., 1998) studies have found lowered benzodiazepine receptor density in amygdala and perihippocampal areas in patients with Panic Disorder. However, GABA abnormalities have also been found in patients with other psychological disorders such as depression (Sanacora et al., 1999) and alcohol dependency (Behar et al., 1999), suggesting once again that these findings may not necessarily be specific to Panic Disorder.

HPA Axis and Autonomic Nervous System Functioning. Dysregulations of the autonomic nervous system and HPA axis have been hypothesized to be central to Panic Disorder. Previous research was mixed, although a carefully controlled examination of corticotropin and cortisol secretions over 24 hours revealed that individuals with Panic Disorder had significantly higher overnight cortisol levels, particularly the more severe

individuals (Abelson & Curtis, 1996). In an attempt to reconcile seemingly contradictory findings, Abelson and colleagues (2006) recently reexamined four HPA studies from their laboratory, including the 24-hour study. They concluded that experimental contexts that are novel, uncontrollable, and/or threatening produce elevated HPA responses in Panic Disorder patients relative to healthy controls and account for disparate findings from previous studies. In other words, they found consistent evidence that individuals with Panic Disorder show elevated HPA reactivity to specific environmental cues, rather than elevated HPA responding in general (i.e., basally). The same effect has been observed with measures of the time course of startle eye blink responding (which is mediated by the amygdala; Anders et al., 2004): baseline startle was enhanced in participants with Panic Disorder relative to controls, but the groups showed otherwise equivalent patterns of responding to approaching shock (Grillon, Ameli, Goddard, Woods, & Davis, 1994). Since baseline represents a state of anticipation about upcoming experimental procedures, the results are interpreted as elevated emotional reactivity to stressful conditions in general versus exaggerated responding to explicit threat cues (Grillon, 2002). Similarly, investigations of autonomic state, such as galvanic skin response, heart rate, respiration, and skin temperature generally indicate that persons with Panic Disorder show an elevated response to experimental contexts versus explicit threat stimuli (e.g., Roth et al., 1992).

Heart rate variability and specifically cardiac vagal tone, the high-frequency component of heart rate variability, have emerged as popular means of assessing parasympathetic responding. High cardiac vagal tone[1] is hypothesized to facilitate the organism's capacity for quick, precise cardiac and behavioral adaptations to changes in internal states and environmental circumstances, whereas low vagal tone limits such flexible responding (Porges, 1992). In Panic Disorder, the evidence for abnormal heart rate variability and vagal tone is mixed. On one hand, compared to nonpanic controls, decreased spectral reserve and high-frequency (HF) power, increased low-frequency (LF) power, and an elevated LF/HF ratio have been found in Panic Disorder samples during both nonpanic and panicogenic conditions (Friedman, Thayer & Borkovec, 1993; Friedman & Thayer, 1998). However, heart rate variability abnormalities have also been found among individuals with Generalized Anxiety Disorder (Thayer, Friedman, & Borkovec, 1996; Thayer et al., 2000), Posttraumatic Stress Disorder (e.g., Cohen et al., 1998, 2000) and Obsessive Compulsive Disorder (Hoehn-Saric, McLeod, & Hipsley, 1995, but see Slaap, Nielen, Boshuisen, van Roon, & den Boer, 2004 for the opposite finding). Thus, it remains unclear whether a distinct pattern of heart rate variability abnormalities characterizes Panic Disorder or whether similar abnormalities generalize across the anxiety disorders. More importantly, multiple well-controlled studies have failed to find heart rate variability differences in Panic Disorder patients versus healthy controls (Asmundson & Stein, 1994; Stein

& Asmundson, 1994; McCraty, Atkinson, Tomasino & Stuppy, 2001; Slaap, et al., 2004) or produce contradictory results (Ito et al., 1999). Differences in time of testing, environmental and psychological conditions surrounding testing (e.g., Abelson et al., 2006), methods of recording and analysis, and subject demographic factors such as age, fitness, illness duration, and severity (e.g., Ito et al., 1999) may account for these inconsistencies.

Researchers also have focused on assessing sympathetic nervous system functioning in Panic Disorder. Evaluations of sympathetic nervous system functioning over extended periods of time in the natural environment have yielded mixed results. Some report no baseline differences between Panic Disorder and nonanxious controls in terms of respiratory and cardiovascular functioning (Clark et al., 1990; Shear et al., 1992), whereas others find differences (Anastasiades et al., 1990; Bystritsky, Craske, Maidenberg, Vapnik, & Shapiro, 1995). A recent study of patients who had remitted from Panic Disorder found evidence for a dysfunctional baroreflex regulation of sympathetic nerve activity before and after audiovisual stimulation (Shioiri et al., 2005). Another study (Lambert et al., 2002) failed to find differences in baroreflex response in Panic Disorder patients versus healthy controls at rest. However, Lambert and colleagues (2002) found evidence of higher reflex gain in arterial baroreflex control of the muscle sympathetic nerve activity in Panic Disorder patients, suggesting increased reactivity of vasoconstricting sympathetic nerves. Differences in the contextual threat value of the studies (anticipating and experiencing stressful stimuli versus resting) perhaps account for these seemingly contradictory findings (see Abelson et al., 2006).

Recently, Alvarenga and colleagues (2006) measured cardiac sympathetic nervous tone during resting baseline via rates of cardiac noradrenaline spillover and found no differences between individuals with and without panic disorder. Rather, they found reductions in measures of the noradrenaline transporter among Panic Disorder patients, suggesting impaired neuronal uptake of noradrenaline in Panic Disorder. Interestingly, Middleton and Ashby (1995) found that Panic Disorder treatment in the form of CBT or imipramine increased plasma noradrenaline, suggesting that noradrenaline-associated dysregulations may be modifiable via treatment.

Despite one discrepant report (Schittecatte, Charles, Depauw, Mesters, & Wilmotte, 1988), the vast majority of studies (e.g., Abelson et al., 1992; Brambilla, Perna, Garberi, Nobile, & Bellodi, 1995) have shown that patients with panic disorder display blunted growth hormone responses to clonodine, an alpha2-adrenoreceptor partial agonist. However, Abelson and colleagues (2005) measured growth hormone secretion over a 24-hour period and found no differences between panic patients and non-patients, suggesting that growth hormone circadian patterns and basal secretory activity are normal in panic disorder. Hence, growth hormone abnormalities in panic disorder may be evidenced only in specific activation paradigms, most consistently with clonodine.

These combined findings have been interpreted as consistent with subsensitivity in post-synaptic alpha2-adrenoreceptor in response to excessive central noradrenergic outflow.

Given the extent of the varied findings across multiple physiological indexes, opinion is mixed regarding whether instability of the autonomic nervous system is a necessary precondition for the development of Panic Disorder, either alone or coupled with cognitive distress (see Stein & Asmundson, 1994 versus Papp, Klein, and Gorman, 1993). As mentioned in the context of heart rate variability studies, the contradictory and inconsistent findings in the physiological literature on Panic Disorder may stem from differences in contextual, methodological, and sample demographic factors. Following the example of Abelson and associates (2006), future research would benefit from investigating hypotheses about specific factors that may account for disparate findings among studies.

Behavioral Features of Panic Disorder

The behavioral features of Panic Disorder involve actions taken or refrained from in order to increase perceived protection from panic attacks. These behaviors can be divided into categories of agoraphobic avoidance, interoceptive avoidance, safety behaviors, and experiential avoidance.

Agoraphobic Avoidance

Behaviors that involve enduring with dread or avoiding places and situations from which escape might be challenging or embarrassing or in which help may not be available in case of a panic attack are illustrations of agoraphobic avoidance (*DSM-IV,* APA, 1994). Typical agoraphobic avoidance behaviors include avoidance of buses or subways, large crowds, shopping malls, restaurants, sporting events, and being alone.

The relationship between agoraphobic avoidance and Panic Disorder remains a subject of debate (e.g., Craske, 2003). Among individuals with Panic Disorder, agoraphobic avoidance ranges widely (Craske & Barlow, 1988). Some individuals manifest few to no agoraphobic symptoms, whereas others spend years as virtual prisoners in their own homes. It is not uncommon for individuals with more severe agoraphobia to limit themselves to a safety zone of a few blocks or miles around their home and to not venture beyond its radius, unaccompanied or at all (Barlow, 2002).

What accounts for these wide discrepancies in the development of agoraphobia among individuals with Panic Disorder? Researchers have examined

various predictors and correlates of agoraphobia. Although agoraphobia tends to increase as history of panic lengthens (Kikuchi et al., 2005), a significant proportion panic for many years without developing agoraphobic limitations. In addition, agoraphobia is not related to age of onset or frequency of panic attacks (Kikuchi et al.; Cox, Endler, & Swinson, 1995; Craske & Barlow, 1988; Rapee & Murrell, 1988). Some investigators have found that panic attack symptomatology is more intense among more agoraphobic individuals (e.g., de Jong & Bouman, 1995; Goisman et al., 1994; Telch, Brouilard, Telch, Agras, & Taylor, 1989; Noyes, Clancy, Garvey, & Anderson, 1987) whereas others fail to find such differences (e.g., Kikuchi et al., 2005; Cox et al., 1995; Craske et al., 1990). Agoraphobic individuals with Panic Disorder do not differ from their nonagoraphobic counterparts in terms of fears of dying, going crazy, or losing control (Cox et al., 1995; Craske, Rapee, & Barlow, 1988). However, individuals with greater agoraphobia show more distress regarding the social consequences of panicking (Amering, Katschnig, Berger, Windhaber, Baischer, & Dantendorfer, 1997; de Jong & Bouman, 1995; Rapee & Murrell, 1988; Telch et al., 1989). A recent investigation by Kikuchi et al. (2005) found that individuals who developed agoraphobia within 6 months of the onset of Panic Disorder had a higher prevalence of Generalized Anxiety Disorder, but not major depression.[2] Whether the latter two findings serve an antecedent or secondary role in agoraphobia remains to be determined.

Occupational status also predicts agoraphobic avoidance, accounting for 18% of the variance: "the more one is forced to leave the house by means of employment, the less one is likely to suffer from agoraphobia" (de Jong & Bouman, 1995, p. 197). But perhaps the strongest predictor of agoraphobia is gender. As agoraphobia increases in severity, the proportion of females increases as well (e.g., Thyer et al., 1985). Socialized sex role expectations and behaviors may contribute to these effects, as socialization may reinforce activity, independence, and confrontation of feared stimuli and situations to a greater extent in boys than girls (Craske & Barlow, 1988; Craske 2003). Given the direct relevance of avoidance behaviors for the development of agoraphobia, the clinical implications are clear.

Interoceptive Avoidance

Strong sensitivity to and avoidance of the internal bodily symptoms associated with anxiety and panic is known as *interoceptive avoidance* (Rapee, Craske, & Barlow, 1995; Bouton, Mineka, & Barlow, 2001; White & Barlow, 2002. Behavioral manifestations include actions intended to minimize exposure to situations, substances, or activities that reproduce bodily sensations associated with symptoms of anxiety and/or panic attacks. Common examples include avoiding exercise, sex, caffeine, alcohol, wearing a necktie, watching arousing or

scary movies, and situations that may produce anger. Assessing the specific interoceptive cues and situations Panic Disorder patients avoid is central to treatment.

Safety Behaviors

Safety behaviors are "behaviors which are intended to avoid *disaster*" (Salkovskis, Clark, Hackman, Wells, & Gelder, 1999, p. 573, italics in original). Within Panic Disorder, they are behaviors that help individuals feel more protected and secure in the event of a panic attack (White & Barlow, 2002). Examples include checking to make sure that a bathroom or hospital is close by, taking one's pulse rate whenever cardiac concerns arise, and carrying cell phones, religious symbols, smelling salts, a special "safe" object, food or drink. Perhaps the most common safety behavior is carrying anti-anxiety medication, including empty pill bottles. Another widespread behavior is bringing along or checking on the location of a safe person, often a spouse, whose presence provides a sense of reassurance that facilitates venturing out to places that otherwise would be avoided. The "safe" person is generally considered as such because they know about the patient's panic attacks and can assist if the panic attack becomes overwhelming (White & Barlow, 2002).

Closely related to the concept of safety behaviors are safety signals, which refer to the safe objects, persons, and situations sought via safety behaviors. These include objects such as empty pill bottles, people such as the therapist or spouse, and situations such as the therapy room, which when present indicate that a given situation is safe from panic-related disaster. An extensive animal literature (see Hermans, Craske, Mineka, & Lovibond, 2006) demonstrates that the presence of safety signals functions as a conditioned inhibitor that interferes with extinction. Though somewhat limited methodologically, a few treatment studies indicate that exposure therapy targeting reductions of safety behaviors and signals is more successful than exposure therapy alone (Salkovskis et al., 1999; Telch, Sloan & Smits, 2000, as cited in Powers, Smits, & Telch, 2004). Also, the mere availability of safety signals rather than the actual use of them disrupted fear extinction in exposure treatment for claustrophobia (Powers, Smits and Telch). Hence, safety behaviors may reduce anxiety in the short term but likely serve to maintain Panic Disorder in the long term by preventing the disconfirmation of the patient's catastrophic predictions about panic (Salkovskis et al., 1999) and/or the extinction of the conditioned response (see Hermans et al., 2006).

Several investigators (Salkovskis et al., 1999; Thwaites & Freeston, 2005) have attempted to differentiate safety-seeking behaviors, which aim to prevent disaster, from adaptive coping strategies that aim to "reduce anxiety alone, with no further fears about the consequences of the anxiety" (Salkovskis et al., 1999, p.

573). However, as noted by Thwaites and Freeston (2005), this distinction is often blurry in practice. Perhaps the most general and clinically relevant definition of safety signals is any behavior intended to avert disasters associated with panic that inhibits corrective learning and eventual fear reduction of anxiety and panic-related stimuli.

Experiential Avoidance

Experiential avoidance occurs when an individual is "unwilling to remain in contact with particular private experiences [e.g., bodily sensations, emotions, thoughts, memories, behavioral predispositions] and takes steps to alter the form or frequency of these events and the contexts" in which they occur (Hayes et al., 1996, p.1154). The types of avoidance discussed thus far, particularly interoceptive avoidance, also may be characterized as *experiential* avoidance. In addition, any form of distraction from anxiety- and panic-related symptoms falls under this category. Distraction behaviors include watching TV, playing video or computer games, and eating, among others. From the perspective of experiential avoidance, distraction represents an unwillingness to experience anxiety- and fear-related thoughts and emotions. Whether distraction interferes with exposure therapy for anxiety is a subject of debate (e.g., Devilly 2001a, 2001b versus Lipke, 2001<AQ: Reference entry needed>; see also Rodriguez & Craske, 1993). However, several controlled, empirical studies (Rodriguez & Craske, 1995; Kamphuis & Telch, 2000; Telch et al., 2004) have found that distraction generally results in less effective fear reduction in the context of exposure therapy.

Experiential avoidance also includes avoidance and suppression of anxiety- and panic-related cognitions, such as "I'm having a heart attack." Evidence generally suggests that thought suppression has a negative impact. That is, thought suppression and to some extent emotional suppression have been shown to be relatively counterproductive, facilitating the return of the very thought or emotional arousal one hoped to avoid (Gross & Levenson, 1993, 1997; Wenzlaff & Wegner, 2000; Richards & Gross, 2000).

Researchers of experiential avoidance argue that psychopathology in general, including Panic Disorder, is caused and maintained by experiential avoidance. In other words, psychopathology stems from an unwillingness to experience whatever thoughts, feelings, memories, and so forth appear in the present (e.g., Hayes et al, 1996, 1999; Eifert & Forsyth, 2005). In claiming that altering thoughts is a form of avoidance, proponents of experiential avoidance argue against attempts to change or modify the content of anxiety- and panic-related thoughts, as is taught in traditional cognitive-behavioral therapy for Panic Disorder (see the following). They argue that psychopathology stems from

unwillingness to accept and remain in contact with present experience. Hence, acceptance of inner experience (e.g., of anxiety- and panic-related thoughts, feelings, and sensations) is promoted over direct modification and change (Hayes et al, 2006; Eifert & Forsyth, 2005; Hayes et al, 1999).

Cognitive Features of Panic Disorder

Persons with Panic Disorder have strong beliefs and fears of physical or mental harm arising from bodily sensations that are associated with panic attacks (e.g., Chambless, Caputo, Bright, & Gallagher, 1984; McNally & Lorenz, 1987). They are more likely to interpret bodily sensations in a catastrophic fashion (Clark et al., 1988), and to allocate more attentional resources to words that represent physical threat, such as "disease" and "fatality" (e.g., Ehlers, Margraf, Davies, & Roth, 1988; Hope, Rapee, Heimberg, & Dombeck, 1990; Asmundson, Sandler, Wilson, & Walker, 1992) and catastrophe words, such as "death" and "insane" (e.g., Maidenberg, Chen, Craske, Bohn, & Bystritsky, 1996; McNally, Riemann, Louro, Lukach, & Kim, 1992). In one dot-probe study that used (what patients believed was) real heartbeat information rather than threat word stimuli, evidence for attentional bias toward the heartbeat stimuli was found in Panic Disorder patients but not healthy controls (Kroeze & van den Hout, 2000). Also, individuals with Panic Disorder are more likely to fear procedures that elicit bodily sensations similar to the ones experienced during panic attacks, including benign cardiovascular, respiratory, and audiovestibular exercises (Zarate, Rapee, Craske, & Barlow, 1988; Jacob, Furman, Clark, & Durrant, 1992) and carbon dioxide inhalations, compared to patients with other anxiety disorders (e.g., Rapee, 1986<AQ: Reference entry needed>; Rapee, Brown, Antony, & Barlow, 1992; Perna, Bertani, Arancio, Ronchi, & Bellodi, 1995) or healthy controls (e.g., Gorman et al., 1994). Patients with Panic Disorder fear signals that ostensibly reflect heightened arousal and false physiological feedback (Ehlers, Margraf, Roth, Taylor, & Birnbaumer, 1988; Craske & Freed, 1995; Craske et al., 2002). The findings are not fully consistent, however, as patients with Panic Disorder did not differ from patients with Social Phobia in response to an epinephrine challenge (Veltman, Zijderveld, Tilders, & Dyck, 1996).

In addition, direct manipulation of appraisals can impact level of distress over physical symptoms. For example, persons with Panic Disorder and nonclinical panickers report significantly less fear and panic during laboratory-based panic provocation procedures, such as hyperventilation and carbon dioxide inhalation, when they perceive that the procedure is safe and/or controllable (e.g., Rapee, Mattick, & Murrell, 1986; Sanderson, Rapee, & Barlow, 1989), when accompanied by a safe person (Carter, Hollon, Carson, & Shelton, 1995), or after cognitive-behavioral treatment that reduces fears of bodily sensations (Craske, Lang, Aikins, & Mystkowski, 2005; Schmidt, Trakowski, & Staab, 1997).

However, manipulations of predictability and controllability did not significantly affect frequency of panic responses among Panic Disorder patients in an epinephrine challenge study (Veltman, Zijderveld, van Dyck, & Bakker, 1998).

Individuals with Panic Disorder sometimes demonstrate memory abnormalities, although the results have been varied and contradictory. Studies of memory bias for physical threat and panic-related words include results supporting the existence of both implicit and explicit memory bias (Cloitre, Shear, Cancienne, & Zeitlin, 1994), explicit but not implicit memory bias (Lundh, Czyzykow, & Ost, 1997; Pauli, Dengler, & Wiedemann, 2005), implicit but not explicit memory bias (Neidhardt & Florin, 1999) and neither type of bias (Rapee, 1994; Baños, Medina & Pascual, 2001). Pauli and colleagues (2005) used event-related brain potentials to investigate implicit memory biases but found no differences between Panic Disorder patients and healthy controls. Differences in experimental methodology and context, instructional sets, sample size, sample demographic, and clinical characteristics may account for differences in these findings.

Recent studies have looked at dual versus single task memory in Panic Disorder patients and compared deficits in Panic Disorder to other anxiety disorders. Among inpatients with severe Panic Disorder (without co-occurring current or past disorders) Lautenbacher and associates (2002) found attentional deficits within a dual-task paradigm for divided attention, but not with a single-task paradigm for selective attention. These deficits also were seen among patients with severe depression (without co-occurring disorders) but not among healthy controls, suggesting that these two severe patient groups show similar deficits in tasks requiring high-attentional load. A small study of memory encoding for social threat and panic-related words found no memory differences between Panic Disorder and Social Phobia patients across various categories of threat encoding, including physical and social threat words (Heinrichs, Hofmann, & Barlow, 2004). The results, which await replication, suggest that threat may be encoded in more general rather than disorder-specific ways in these anxiety disorders. Alternatively, disorder-specific differences in memory encoding may require a larger sample size or more powerful manipulation of memory categories.

Studies utilizing event-related brain-potential EEG methodologies provide a more precise understanding of the time course of panic-related attentional and memory abnormalities. In contrast to healthy controls, panic patients failed to modulate prefrontal event-related brain potentials when responding to words with different affective connotations in a memory recognition task (Windmann, Sakhavat, & Kutas, 2002). The effect was found in the latency range of responding (300–500ms), which generally assumes greater influence of autonomic rather than controlled memory processes, but not at later processing stages (700ms+). Hence, the authors suggest that patients may "adopt conscious strategies to minimize the impact of these early processing abnormalities on overt behaviors" (p. 357). On a cautionary note, half of the patients had mild depression, making it unclear

whether the results were due to panic- or depression-related functioning (or both). In a related set of findings, Pauli and colleagues (2005) found that panic patients—but not healthy controls—showed early enhanced brain potentials (at 100–200ms and 200 to 400ms) in response to panic-related words. The authors concluded that Panic Disorder may be characterized by an early, efficient, largely automatic processing bias toward panic-related stimuli.

Whereas event-related brain potential studies help identify the timing of cognitive processing abnormalities, fMRI brain imaging studies reveal their location. A small fMRI study of visual exposure to physical threat and neutral words (Maddock, Buonocore, Kile & Garrett, 2003), found that individuals with Panic Disorder showed greater activity in the left posterior cingulate and dorsolateral frontal cortices during threat words than healthy controls. The authors associated these brain regions with the link between affect and verbal memory processing, consistent with the notion of greater memory processing for threat-related words in Panic Disorder. However, memory for threat words was not tested directly. In an fMRI study of neuroanatomical correlates of the Stroop task across Panic Disorder, Obssessive-Compulsive Disorder (OCD), and hypochondriasis patient groups (van den Heuvel et al., 2005), panic patients showed activation patterns similar to hypochondriacal patients. Specifically, both patient groups displayed increased ventral and dorsal brain region activation, suggesting increased unconscious emotional processing as well as increased cognitive elaboration. The study generally did not find Panic Disorder-specific neuroanatomical correlates; rather, results differentiated a shared panic and hypochondriasis patient pattern from that of OCD patients. The grouping of results may reflect the exaggerated concern over body-related sensations shared by panic and hypochondriasis patients.

Emotional Features of Panic Disorder

The temperament variable most associated with anxiety disorders, including Panic Disorder, is neuroticism (Eysenck, 1967; Gray, 1982a, 1982b), or proneness to experience negative emotions in response to stressors. A closely linked construct is *negative affectivity*, or the tendency to experience an array of negative emotions across a variety of situations, even in the absence of objective stressors (Watson & Clark, 1984). Structural analyses confirm that negative affect is a higher-order factor that distinguishes each anxiety disorder and depression from controls with no mental disorder. The anxiety disorders load differentially on negative affectivity, with more pervasive anxiety disorders such as Generalized Anxiety Disorder loading more heavily, Panic Disorder loading at an intermediate level, and Social Anxiety Disorder loading the least (Brown et al., 1998).[3] Lower-order factors further discriminate among the anxiety disorders, with fear of fear

being the factor that discriminates Panic Disorder from other anxiety disorders (Brown, Chorpita, & Barlow, 1998; Zinbarg & Barlow, 1996).

Longitudinal prospective evidence for the role of neuroticism in predicting the onset of Panic Disorder is relatively limited. However, neuroticism was found to predict the onset of panic *attacks* (Hayward, Killen, Kraemer, & Taylor, , 2000; Schmidt, Lerew & Jackson, 1997, 1999), and emotional reactivity at age 3 was a significant variable in the classification of Panic Disorder in 18- to 21-year-old males (Craske, Poulton, Tsao, & Plotkin, 2001). Ongoing studies, such as the Northwestern/UCLA Youth Emotion Project, are currently evaluating the relationships among neuroticism, various other risk factors, and Panic Disorder.

Interaction with Environmental Factors

Environmental factors often interact with biologically and genetically related temperamental factors to increase risk for anxiety disorders, including Panic Disorder. Several environmental factors are reviewed in the following section. Early caregiving and parenting likely relate more to risk for psychopathology in general, whereas abuse and especially childhood experiences with illness may relate more specifically to Panic Disorder. Also, depending on their nature, life stressors may play a general or more direct role in the etiology and maintenance of Panic Disorder.

Early Caregiving and Infant Attachment

Emerging research supports the hypothesis that early experiences with infant care may play an important role in buffering or facilitating later proneness toward anxiety. Specifically, early experiences with prediction and control may be associated with the development of adaptive emotional regulatory capacities in the face of negative stressors. In the context of emotional regulation in infants and children, prediction refers to a contingency (cause-effect) awareness of events in the environment as well as prediction of outcomes by virtue of one's own responding, and control refers to control over emotions and outcomes via one's own attention and behaviors (Craske, 2003). Evidence (e.g.. Papousek & Papousek, 1997, 2002; Rochat & Striano, 1999) supports the assertion that parental monitoring and reactivity to infant signals enable infants to learn contingency-response relationships and hence, a sense of predictability. Initially, a sense of predictability may develop from the relationship between an infant's cues and the caretaker's response. Later, this may transfer to contingency knowledge of the relationship between an infant's own behaviors and responses (see Craske, 2003). According to attachment pioneer Bowlby (1969, 1980), caregiver responses

that are characterized by unpredictability and unresponsiveness may lead to anxious attachment in which the child is chronically insecure and apprehensive.

However, this theorizing remains largely speculative since experimentally manipulating predictability and control for extended periods of time in infant humans is not ethically possible. Hence, the most compelling evidence of the effects of prolonged lack of predictability and control in infants comes from research with rhesus monkeys. Mineka, Gunnar, and Champoux (1986) demonstrated that infant rhesus monkeys who were granted control over toys and food habituated more quickly to novel stimuli, demonstrated more exploratory behavior in a novel playroom, and demonstrated enhanced coping responses during separation from peers compared to infants without control (but with equal exposure) over toys and food. In the same sample, administration of benzodiazepine inhibitors resulted in increased distress and avoidance among the no control group, whereas the control group showed greater aggression. Mineka and Cook (1986) concluded that experiences with mastery and control buffer the effects of stressful experiences. Longitudinal studies of very young children are needed to more directly establish the link between early caregiving, predictability, and controllability, and subsequent stress reactivity.

Parenting

The literature on infant attachment (Bowlby 1969, 1980) and developmental models of anxiety (Craske, 1999, 2003) predicts that anxious, insecure attachment between caregiver and infant places the infant at risk for chronic emotional regulatory difficulties, including anxiety. General parental styles across situations may contribute to childhood trait anxiety, whereas situationally specific parental behaviors may contribute to the development of particular anxiety disorders in children (Craske, 1999). Although many previous studies examining these hypotheses are fraught with methodological difficulties, more recent studies on parent-child interactions with anxious children and/or anxious parents have been more informative. Though not specific to Panic Disorder, the research on parenting illuminates one risk factor for anxiety disorders in general.

One interesting line of studies examines children's current perceptions of their parents' behavior. Generally, children of anxious parents view their families as more conflictual, less independent, less cohesive, and more controlling than children with healthy, nonanxious parents (see Whaley, Pinto, & Sigman, 1999). In addition, children with anxiety disorders view their families as less independence promoting than non-anxious children. Another study has demonstrated that perceptions of low maternal caring and overprotectiveness were highest among children with anxiety disorders, slightly lower among high trait

anxious children and lowest among low trait anxious children (Bennet & Stirling, 1998). These studies, however, are limited by reliance on self-report measures and cross-sectional designs, and they only assess influences of state anxiety on perceptions of family functioning (see Craske, 2003; Wood, McLeod, Sigman, Hwang, & Chu, 2003). Thus, little conclusive evidence exists for linking self-reported parenting style to offspring anxiety (Wood et al.).

A more reliable body of research relies on behavioral coding of observed parent-child interactions. Fortunately, the findings generally converge with the self-report data. A descriptive review by Wood et al. (2003) concluded that observed parental control during parent-child interactions (defined as overprotectiveness, excessive regulation of activities, routines, and decision making) consistently was associated with child shyness and childhood anxiety disorders. Of note, the Wood et al. review did not include a study by Woodruff-Borden, Morrow, Bourland, & Cambron (2002), which found that parents with anxiety disorders were less engaged and more withdrawn though not more controlling than nonanxious parents. Wood et al. (2003) found mixed evidence for associations between parental acceptance (e.g., warmth, praise, active listening, responsiveness) and modeling of anxious behaviors (e.g., catastrophizing, emphasizing danger/ threat, punishing coping behaviors) and childhood anxiety. Finally, Wood et al. (2003) concluded that the directionality and hence causality of the parent-child interactions remains to be determined. Furthermore, the specificity of parental behaviors to risk for anxiety disorders has not yet been demonstrated.

Hudson and Rapee (2001) have suggested that overinvolvement may represent a general parenting response to children who tend toward distress and psychopathology rather than to anxious children in particular. However, more evidence is needed to elucidate disparate findings. For example, Hudson and Rapee observed that mothers of anxious children were more negative, overinvolved, and intrusive than mothers of nonanxious control children. Similar to several other studies (e.g., Hibbs, Hamburger, Kruesi, & Lenane, 1993; but see Stubbe, Zahner, Goldstein, & Leckman, 1993, for the opposite finding), they failed to find a difference in maternal behaviors toward children with anxiety disorders versus children with oppositional disorders. Perhaps the most thorough attempt at disentangling the impact of child and maternal anxiety in a clinical sample is work by Whaley and Sigman (Whaley, Pinto & Sigman, 1999; Moore, Whaley, & Sigman, 2004). In comparison with nonanxious control mothers, anxious mothers were observed to criticize and catastrophize more, and to display less warmth and autonomy-granting toward their children. Maternal behaviors predicted children's anxiety levels, and children's anxiety levels predicted maternal autonomy-granting (Whaley et al., 1999). Finally, mothers of anxiety-disordered children, regardless of their own anxiety status, displayed less warmth and autonomy-granting (Moore et al., 2004). Though limited by cross-sectional

design, these findings support an interactive model in which parenting behaviors predict offspring anxiety and offspring anxiety molds parenting behaviors.

Childhood Experiences with Illness and Abuse

Childhood experience with medical illness, personally or via observing others, may increase the risk for the subsequent development of anxiety disorders in general and Panic Disorder in particular. Experience with personal respiratory disturbance and parental illness in childhood predicted Panic Disorder onset at ages 18 or 21 in a large, longitudinal sample (Craske et al., 2001). This finding is consistent with reports of more respiratory disturbance in the history of Panic Disorder patients compared to other anxiety-disordered patients (Verburg, Griez, Meijer & Pols, 1995). Furthermore, a recent study found that first-degree relatives of Panic Disorder patients had a significantly higher prevalence of chronic obstructive respiratory disease and asthma, in particular, compared with first-degree relatives of patients with other anxiety disorders (van Beek, Schruers, & Friez, 2005).

Childhood experiences of sexual and physical abuse may also prime Panic Disorder. Retrospective reports of childhood abuse were associated with Panic Disorder onset at ages 16–21 in a recent longitudinal analysis of New Zealanders from birth to age 21 (Goodwin et al., 2005), a finding consistent with multiple cross-sectional studies in both clinical and community samples (e.g., Bandelow et al., 2002; Kendler et al., 2000; Kessler et al., 1997; Stein et al., 1996; Moisan & Engels, 1995). The link with childhood abuse was stronger for Panic Disorder than for other anxiety disorders such as Social Phobia (Safren et al., 2002; Stein et al., 1996) and Obsessive-Compulsive Disorder (Stein et al., 1996). In addition, some studies found an association between Panic Disorder and exposure to violence between other family members, usually interparental violence (e.g., Moisan & Engels, 1995; Bandelow et al., 2002), whereas the most recent study did not (Goodwin et al, 2005). Retrospective reporting of childhood abuse in all of these studies, however, limits their findings.

Stress

The relationship between external aversive events, also known as *stressful* events, and Panic Disorder has several facets. First, temperamental vulnerabilities, such as neuroticism, may contribute to more frequent and more potent stressful life events (Craske, 2003). Second, stressful life events may precipitate initial panic attacks and contribute to their repeated occurrence over time: As described earlier, a large percentage of individuals with Panic Disorder report the presence of identifiable stressors around the time of the first panic attack (Craske et. al.,

1990; Faravelli & Pallanti, 1989; Pollard et al., 1989; Roy-Byrne, Geraci, & Uhde, 1986; although see Rapee, Litwin, & Barlow, 1990 for contradictory findings). As alluded to earlier, significant childhood adversity and stressful life events are both associated with increased risk for anxiety disorders as well as other psychopathology (Benjamin, Costello, & Warren, 1990; Brown, Harris, & Eales, 1993; Kessler et al., 1997). In addition, variations in anxiety symptom levels over time are influenced by life stress and other environmental factors (Mackinnon, Henderson, & Andrews, 1990). In addition, life stressors over multiple months and years predicted later anxious and depressive symptoms in adult (Cohen, McGowan, Fooskas, & Rose, 1984) though not adolescent samples (Cohen, Burt, & Bjork, 1987; Rueter, Scaramella, Wallace, & Conger, 1999).

A stress-diathesis perspective would hypothesize that stressful life events interact with preexisting vulnerabilities to produce panic attacks and Panic Disorder. For example, autonomic instability (e.g., the tendency to experience cardiac symptoms and shortness of breath) may develop into full-blown panic when instances occur in threatening contexts or following life stressors, when the sensations are more likely to be perceived as threatening (Craske, 1999). According to Bouton, Mineka, and Barlow (2001), evidence suggests that high anxiety elevates the likelihood of panic attacks. Hence, stressful life events may elevate levels of anxiety, particularly in vulnerable individuals, which in turn, increases the risk for panic. From a related perspective, a recent epidemiological study in a Russian sample examined the interaction of anxiety sensitivity, or the tendency to interpret anxiety symptoms as dangerous and threatening, and recent exposure to stressful life events (Zvolensky, Kotov, Antipova, & Schmidt, 2005). The study found that high levels of stressful life events interacted with a subscale of anxiety sensitivity (the physical concerns subscale) to predict panic attacks in the past week, and agoraphobic avoidance, beyond levels of negative affect. Their findings are consistent with a stress-diathesis model. However, the general notion of stress-diathesis does not offer specificity in the etiology of Panic Disorder relative to other anxiety disorders.

Etiological Models of Panic Disorder

Barlow (1988; Barlow, Chorpita, & Turovsky, 1996) characterizes panic attacks as "false alarms," in which a fight-or-flight response is triggered in the absence of threatening stimuli. False alarms in the form of panic attacks occur relatively commonly in the general, nonclinical population (e.g., Wittchen & Essau, 1991; Norton, Cox, & Malan, 1992). This finding begs the question: What accounts for the difference between the majority of individuals, who display little to no distress over panic attacks, versus the minority, who develop Panic Disorder?

As described earlier, neuroticism is viewed as a higher-order factor characteristic of all anxiety disorders, with fear of fear being more singular to Panic Disorder. The construct of fear of fear overlaps with the construct of anxiety sensitivity, or the belief that anxiety and its associated symptoms may cause deleterious physical, social, and psychological consequences that extend beyond any immediate physical discomfort during an episode of anxiety or panic (Reiss, 1980). Anxiety sensitivity is elevated across most anxiety disorders, but it is particularly elevated in Panic Disorder (e.g., Taylor, Koch, & McNally, 1992; Zinbarg & Barlow, 1996), especially the physical concerns subscale (Zinbarg, Barlow, & Brown, 1997; Zinbarg & Barlow, 1996). Therefore, beliefs that physical symptoms of anxiety are harmful seem to be particularly relevant to Panic Disorder.

Anxiety sensitivity may be acquired insidiously from a lifetime of direct aversive experiences (such as personal history of significant illness or injury), vicarious observations (such as exposure to significant illnesses or death among family members, or family members who display fear of body sensations through hypochondriasis), and/or informational transmissions (such as parental warnings or overprotectiveness regarding physical well being; Craske & Rowe, 1997). In support, Watt, Stewart, and Cox (1998) reported that levels of anxiety sensitivity in young adulthood were positively correlated with retrospectively reported instrumental and vicarious conditioning experiences in childhood. Specifically, individuals with high anxiety sensitivity reported more learning experiences related to anxiety symptoms in the form of parental reinforcement (instrumental) and parental modeling (classical). Similarly, Watt and Stewart (2000) found that elevated anxiety sensitivity related to retrospectively reported parental responses to somatic symptoms in general but not specifically to anxiety-related symptoms. Unfortunately, data from all of these studies are retrospective and thus vulnerable to biased recall.

Anxiety sensitivity is posited to be a risk factor for Panic Disorder because it primes reactivity to bodily sensations. Consistent with this view is the finding that anxiety sensitivity predicts subjective distress and reported symptomatology in response to procedures that induce strong physical sensations such as carbon dioxide inhalation (Forsyth, Palav, & Duff, 1999), balloon inflation (Messenger & Shean, 1998), and hyperventilation (Sturges, Goetsch, Ridley, & Whittal, 1998), in nonclinical samples, even after controlling for the effects of trait anxiety (Rapee & Medoro, 1994). In addition, several longitudinal studies indicate that high scores on the Anxiety Sensitivity Index predict the onset of panic attacks over 1- to 4-year intervals in adolescents (Hayward, Killen, Kraemer, & Taylor, 2000), college students (Maller & Reiss, 1992), and community samples with specific phobias or no anxiety disorders (Ehlers, 1995). The predictive relationship remains after controlling for prior depression (Hayward, Killen, Kraemer & Taylor, 2000). In addition, Anxiety Sensitivity Index scores predicted spontaneous panic attacks

and worry about panic during an acute military stressor (i.e., 5 weeks of basic training), even after controlling for history of panic attacks and trait anxiety (Schmidt, Lerew, & Jackson, 1997, 1999).

However, Bouton et al. (2001) argue that the relationship between anxiety sensitivity and panic attacks in these studies is relatively small, not exclusive to panic, and is weaker than the relationship between panic and general neuroticism. Furthermore, these studies have not evaluated the prediction of the development of full Panic Disorder as opposed to panic attacks.

Two other models offer accounts for the persistence of fear of bodily sensations. The first model, put forth primarily by Clark (1986, 1988, 1996), is cognitive in nature. Clark and others (e.g., Salkovskis, 1988) argue that catastrophic misappraisals of bodily sensations, including misinterpretation of panic- and anxiety-related bodily sensations as signs of imminent death, craziness, loss of control, and so forth, are central to the development and maintenance of Panic Disorder. As reviewed earlier, there is extensive evidence that persons with Panic Disorder judge certain bodily sensations to be detrimental. However, Bouton et al. (2001) take issue with Clark's cognitive misappraisal model for multiple reasons, including the fact that the model cannot account for panic attacks that lack conscious cognitive appraisal (e.g., nocturnal panic), without becoming untestable. They also note that although catastrophic cognitions often occur in panic patients, they do not necessarily play a causal role in Panic Disorder. Finally, Bouton et al. critique the cognitive model for not specifying how and when such cognitions are acquired and for whom and under what circumstances they become catastrophic.

The second model was initially put forth by Eysenck more than four decades ago (Eysenck 1960; Eysenck & Rachman, 1965), expanded by Goldstein and Chambless (1978) and recently brought up to date by Bouton et al. (2001). This model emphasizes interoceptive conditioning, or the process by which low-level somatic sensations of arousal or anxiety (e.g., elevated heart rate or perspiration) become conditioned stimuli due to their association with intense fear, pain, or distress (Razran, 1961). In the context of Panic Disorder, the result is that early somatic components of the anxiety response come to elicit significant bursts of anxiety or panic. An extensive body of experimental literature attests to the robustness of interceptive conditioning (e.g., Dworkin & Dworkin, 1999), particularly with regard to early interoceptive drug onset cues becoming conditioned stimuli for larger drug effects (e.g., Sokolowska, Siegel, & Kim, 2002). In addition, interoceptive conditioned responses are not dependent on conscious awareness of triggering cues (Razran, 1961) and are observed even under anesthesia in animals (e.g., Lennartz & Weinberger, 1992; Shibuki, Hamamura, & Yagi, 1984; Uno, 1970) and humans (e.g., Block, Ghoneim, Fowles, Kumar, & Pathak, 1987). Within this model, slight changes in relevant bodily functions that are not consciously recognized may elicit conditioned fear

and panic due to previous pairings with the terror of panic (Barlow, 1988; Bouton, Mineka, & Barlow, 2001). Nevertheless, some researchers argue that the acquisition of interoceptive conditioned responding requires conscious awareness (Irie, Maeda, & Nagata, 2001; Lovibond & Shanks, 2002).

Expanding on this view, Bouton et al. (2001) argue that the similarity between conditioned and unconditioned stimuli creates very strong, easily conditioned responses, as occurs when initial bodily symptoms of panic (conditioned stimulus) signal the rest of the panic attack (unconditioned stimulus). Drawing on the extensive animal and human learning literature, they explain that interoceptive cues do not always produce conditioned panic due to factors such as the presence of safety signals and context effects (e.g., performance in one context does not always generalize to performance in another context). In addition, they cite evidence from Öhman and Mineka (2001) and others (e.g., LeDoux, 1996) to argue against the notion that conditioning necessarily involves propositional knowledge and cognitive awareness. Rather, Bouton et al. (2001) argue that catastrophic misappraisals may accompany panic attacks because they are part of the range of responses linked to panic or because they have been encouraged or reinforced. Such thoughts may become conditioned stimuli that trigger anxiety or they may simply be part of the conditioned response to anxiety- and panic-related cues.

Assessment of Panic Disorder

Interviews

An in-depth interview is the first step in establishing diagnostic and behavioral-cognitive profiles. The value of structured interviews lies in their contribution to differential diagnosis and interrater reliability. Several semi- and fully structured interviews exist. The Schizophrenia and Affective Disorders Schedule-Life Time Version (Anxiety Modified) produces reliable diagnoses for most of the anxiety disorders (Generalized Anxiety Disorder and simple phobia being the exceptions Manuzza et al., 1989), as does the Structured Clinical Interview for *DSM-IV,* which covers all of the mental disorders (First, Spitzer, Gibbon, & Williams, 1994). However, the semistructured interview that most specifically focuses on assessment and differential diagnosis among the anxiety disorders is the Anxiety Disorders Interview Schedule-Fourth Edition (ADIS-IV; DiNardo, Brown, & Barlow, 1994). In addition to its primary focus on anxiety

disorders, the ADIS-IV also evaluates mood disorders and somatoform disorders, as well as screens for psychotic and drug conditions. Differential diagnosis among the anxiety disorders is sometimes difficult because, as described earlier, panic is a ubiquitous phenomenon (Barlow, 1988), occurring across a wide variety of emotional disorders. It is not uncommon for persons with specific phobias, Generalized Anxiety Disorder, Obsessive-Compulsive Disorder, and Posttraumatic Stress Disorder to report panic attacks. Hence, the ADIS-IV facilitates a reliable method of gathering information to make differential diagnoses among the anxiety disorders and also offers the ability to distinguish between clinical and subclinical presentations of a disorder. Interrater agreement ranges from satisfactory to excellent for the various anxiety disorders using this instrument (Brown, DiNardo, Lehman, & Campbell, 2001).

Clinical Rating Scales

There are no clinical rating scales specific to Panic Disorder and agoraphobia. However, a clinical rating of severity of distress and disablement (CSR; 0 = not at all, 8 = extreme) is often made based on the information gathered from the diagnostic interview. A CSR rating of 4 or higher indicates that the individual meets diagnostic criteria for a given disorder and evidences clinically significant distress and/or disablement stemming from the disorder. With proper training procedures, adequate reliabilities have been demonstrated for clinical severity ratings from the ADIS-IV interview (Brown, DiNardo, Lehman, & Campbell, 2001).

Self-Report and Behavioral Measures

Several standardized self-report inventories provide useful information for treatment planning, as well as being sensitive markers of therapeutic change. The Anxiety Sensitivity Index (Reiss, Peterson, Gursky, & McNally, 1986) has received wide acceptance as a trait measure of threatening beliefs about bodily sensations. It has good psychometric properties and tends to discriminate Panic Disorder from other types of anxiety disorders (e.g., Taylor, Koch, & McNally, 1992; Telch, Sherman, & Lucas, 1989). More specific information about which particular bodily sensations are feared the most, and what specific misappraisals occur most often, can be obtained from the Body Sensations and Agoraphobia Cognitions Questionnaires (Chambless, Caputo, Bright & Gallagher, 1984). Extensive psychometric and clinical research indicates that these questionnaires show strong psychometric properties (Chambless et al., Arrindell, 1993), discriminate between individuals with panic and agoraphobia versus other anxiety disorders (Chambless & Gracely, 1989), and are sensitive to change

following treatment (Chambless et al., 1984). Fears of interoceptive stimuli (e.g, caffeine, exercise) can be measured by the Albany Panic and Phobia Questionnaire, which has demonstrated good to excellent Cronbach alphas and adequate test-retest reliability (Rapee, Craske, & Barlow, 1995). The Mobility Inventory (Chambless, Caputo, Jasin, Gracely, & Williams, 1985) lists agoraphobic situations that are rated based on degree of avoidance, when alone, and when accompanied. This instrument is useful for establishing in vivo exposure hierarchies. Finally, Newman and colleagues (2006) recently developed the Panic Disorder Self-Report (PDSR), a self-report diagnostic measure based on *DSM-IV* Panic Disorder criteria. The PDSR demonstrates excellent sensitivity and specificity in diagnosing Panic Disorder, strong agreement with a structured diagnostic interview, and good retest reliability and convergent and discriminant validity (Newman et al., 2006).

Behavioral Tests

The behavioral test is a useful measure of degree of avoidance of specific situations. Behavioral approach tests can be standardized or individually tailored. The standardized behavioral test for agoraphobia usually involves walking or driving a particular route, such as a 1-mile loop around the clinic setting. Anxiety levels are rated at regular intervals and actual distance walked/driven is measured. The disadvantage is that the specific task may not be relevant to all clients, and hence, the value of individually tailored tasks that usually entail attempts at three to five individualized situations that the client has identified as being anywhere from somewhat to extremely difficult. These might include driving two exits on a freeway, waiting in a bank line, or shopping in a local supermarket for 15 minutes. Maximum levels of anxiety and degree of approach (i.e., refused task, attempted but escaped from task, or completed task) are assessed for each situation. Individually tailored behavioral tests are more informative for clinical practice, although they confound between-subject comparisons for research purposes. Standardized behavioral tests for individuals with Panic Disorder target interoceptive sensations and typically include exercises such as spinning, running in place, and hyperventilating. As with the behavioral tests for agoraphobia, anxiety levels are recorded continuously along with the duration for which the client continued each exercise.

Standardized and individually tailored behavioral tests are susceptible to demand biases for fear and avoidance prior to treatment and for improvement after treatment (Borkovec, Weerts, & Bernstein, 1977). On the other hand, behavioral tests are an important supplement to self-report of agoraphobic avoidance because clients tend to underestimate what they can actually achieve (Craske, Rapee, & Barlow, 1988). In addition, behavioral tests often reveal information of which the individual is not fully aware, and yet is important for

treatment planning. For example, the safety-seeking behavior of remaining close to supports such as railings or walls may not be apparent until observing the client walk through a shopping mall.

Ongoing Assessment

Self-monitoring is a very important part of assessment and treatment for Panic Disorder and agoraphobia. Retrospective recall of past episodes of panic and anxiety, especially when made under anxious conditions, may inflate estimates of panic frequency and intensity (Margraf et al., 1987; Rapee, Craske, & Barlow, 1990). Moreover, such inflation may contribute to apprehension about future panic. Thus, to the degree that ongoing self-monitoring yields more accurate, less inflated estimates, it is a therapeutic tool (see Craske & Tsao, 1999, for a comprehensive review of self-monitoring for panic and anxiety). Also, ongoing self-monitoring is believed to contribute to increased objective self-awareness that is essential to cognitive behavioral therapy approaches.

To assess the course and rate of change in treatment, as well as to investigate the mechanisms or mediators by which a given treatment exerts its effects (see Kraemer et al., 2002), it also is important to include psychometrically sound assessment of anxiety symptoms during treatment. Ongoing measures, also known as *process measures,* can be administered to patients at regular intervals during treatment to assess changes in panic symptomology. The Anxiety Sensitivity Index (Reiss et al., 1986) is one example of an appropriate symptom process measure for treatment of panic disorder. Finally, particularly at treatment follow-up, assessments may benefit from including broader quality of life (QOL) measures that capture the wider impact of Panic Disorder treatment. For example, the Quality of Life Inventory (Frisch, Cornell, Villanueva, & Retzlaff, 1992) assesses seventeen domains including the quality of clients' family relationships, friendships, and sense of meaning and life direction, whereas the frequently used, well-validated SF–36 (Ware, 1993; McHorney, Ware & Raczek, 1993) assesses physical functioning, mental health, social functioning, vitality, and general health.

Neurobiological Assessment

A medical evaluation is generally recommended because several medical conditions should be ruled out before assigning the diagnosis of Panic Disorder and agoraphobia. These include thyroid conditions, caffeine or amphetamine intoxication, drug withdrawal, or pheochromocytoma (a rare, adrenal gland tumor). Furthermore, certain medical conditions can exacerbate Panic Disorder and agoraphobia, although panic and agoraphobia are likely to continue even when they are under medical control. Mitral valve prolapse, asthma,

allergies, and hypoglycemia fall into this category. These medical conditions exacerbate Panic Disorder and agoraphobia to the extent that they elicit the types of physical sensations that are feared. For example, mitral valve prolapse sometimes produces the sensation of a heart flutter, asthma produces shortness of breath, and hypoglycemia produces dizziness and weakness.

Ongoing physiological measures are not very practical tools for clinicians, but can provide important information. In particular, the discrepancy described earlier between reports of symptoms and actual physiological arousal can serve as a therapeutic demonstration of the role of attention and appraisal in symptom production. Similarly, actual recordings provide data to disconfirm misappraisals such as "my heart feels like its going so fast that it will explode" or "I'm sure my blood pressure is so high that I could have a stroke at any minute." Finally, baseline levels of physiological functioning, which are sometimes dysregulated in anxious individuals, may be sensitive measures of treatment outcome (e.g., Craske et al., 2005).

Interventions

Psychological

The most widely studied and validated psychotherapeutic treatment for Panic Disorder is cognitive-behavioral therapy (CBT) in its various forms. The two major forms of CBT have been Barlow and Craske's Panic Control Treatment (PCT), and Clark's cognitive therapy for panic. Both treatments emphasize components of psychoeducation about panic to correct misconceptions regarding panic symptoms, cognitive restructuring to identify and correct distortions in thinking, and interoceptive exposure to feared bodily sensations (e.g., palpitations, dyspnea, dizziness) and in vivo exposure to feared situations (e.g., unfamiliar areas, driving) to obtain corrective information that disconfirms fearful misappraisals and eventually lessens fear responding. Breathing retraining as a means for helping patients cope with panic and anxiety is sometimes included. Although PCT and Clark's cognitive therapy for Panic Disorder have not been directly compared, the major difference lies in the reliance of PCT on both cognitive and conditioning models, with behavioral exposure functioning as a primary agent of therapeutic change. In Clark's model, cognitive models are more central and behavioral exposure serves as a vehicle for cognitive change.

Results for both of these forms of CBT typically yield panic-free rates in the range of 70% to 80% of those treated and high end-state rates (i.e., within

normative ranges of functioning) in the range of 50% to 70% (e.g., Barlow, Craske, Cerny, & Klosko, 1989; Clark et al., 1994). Two meta-analyses reported very large effect sizes of 1.55 and 0.90 for CBT for panic disorder (Mitte, 2005; Westen & Morrison, 2001). Also, results generally are maintained over follow-up intervals for as long as 2 years (Craske, Brown, & Barlow, 1991). This contrasts with the higher relapse rates typically found with medication approaches to the treatment of panic disorder, particularly high-potency benzodiazepines (e.g., Gould, Otto & Pollack, 1995). One analysis of individual profiles over time suggested a less optimistic picture, in that one third of clients who were panic-free 24 months after CBT had experienced a panic attack in the preceding year, and 27% had sought additional treatment for panic over that same interval of time (Brown & Barlow, 1995). Nevertheless, this approach to analysis did not take into account the general trend toward continuing improvement over time. Thus, rates of eventual therapeutic success may be underestimated when success is defined by continuous panic-free status since the end of active treatment.

The effectiveness of CBT extends to patients who experience nocturnal panic attacks (Craske et al., 2005). Also, CBT has proven very helpful in lowering relapse rates upon discontinuation of high-potency benzodiazapines (e.g., Otto, Pollack, Sachs, Reiter, Meltzer-Brody, & Rosenbaum, 1993; Spiegel, Bruce, Gregg, & Nuzzarello, 1994). Moreover, treatment is effective even when there is comorbidity; indeed, some studies indicate that comorbidity does not reduce the effectiveness of CBT for Panic Disorder (e.g., Brown, Antony, & Barlow, 1995; McLean et al., 1998). Furthermore, CBT results in improvements in comorbid conditions (Brown, Antony & Barlow, 1995; Tsao, Lewin, & Craske, 1998; Tsao, Mystkowski, Zucker, & Craske, 2002, 2005). In other words, co-occurring symptoms of depression and other anxiety disorders tend to improve after CBT for panic disorder. However, one study assessing patients 2 years after treatment suggests that the benefits for comorbid conditions may lessen over time (Brown et al., 1995). Nonetheless, the general finding of improvement in comorbidity suggests the value of remaining focused on Panic Disorder treatment even when comorbidity is present, since the comorbidity will be benefited as well (for at least up to 1 year). In fact, there is preliminary evidence to suggest that attempting to simultaneously address panic disorder along with comorbidity (using CBT, tailored to each disorder) may be less effective on average than remaining focused on Panic Disorder (Craske et al., in press), although this finding is in need of replication.

Generally, CBT for agoraphobia involves more situational exposure than CBT for Panic Disorder alone. Randomized controlled studies of CBT for agoraphobia generally yield slightly less effective results than CBT for Panic Disorder with no or minimal agoraphobia (e.g., Williams & Falbo, 1996). Nonetheless, the trends suggest continuing improvement over time, after CBT is over. Furthermore, Fava, Zielezny, Savron, and Grandi (1995) found that only

18.5% of their panic-free clients relapsed over a period of 5 to 7 years after exposure-based treatment for agoraphobia. Some research suggests that the trend for improvement after acute treatment is facilitated by involvement of significant others in every aspect of treatment (e.g., Cerny, Barlow, Craske, & Himadi, 1987). Recently, an intensive 8-day treatment, using a sensation-focused PCT approach was developed for individuals with moderate to severe agoraphobia, and initial results are promising (Morissette, Spiegel, & Neinrichs, 2005).

Attempts have been made to dismantle the different components of CBT for panic and agoraphobia. The results are somewhat confusing, and depend on the samples used (e.g., mild versus severe levels of agoraphobia) and the exact comparisons made. It appears that the cognitive therapy component may be effective (e.g., Williams & Falbo, 1996) even when conducted in full isolation from exposure and behavioral procedures (e.g., Salkovskis, Clark, & Hackman, 1991), and is more effective than applied relaxation with exposure (e.g., Arntz & van den Hout, 1996; Clark et al., 1994). On the other hand, some studies find that cognitive therapy does not improve outcome when added to in vivo exposure treatment for agoraphobia (e.g., van den Hout, Arntz, & Hoekstra, 1994; Rijken, Kraaimaat, Ruiter, & Garssen, 1992). A recent meta-analysis (Chambless & Peterman, 2004<AQ: Reference entry needed>) found no differences between CBT and behavioral therapies in the treatment of Panic Disorder. It appears that exposure alone, without the aid of tools such as cognitive restructuring or relaxation training, is effective for Panic Disorder and agoraphobia (e.g. Rijken, Kraaimaat, de Ruiter, & Garssen, 1992; van den Hout, Arntz, & Hoekstra, 1994). Another study found that breathing skills training and repeated interoceptive exposure to hyperventilation did not improve outcome beyond in vivo exposure alone for agoraphobia (de Beurs, van Balkom, Lange, Koele, & van Dyke, 1995), and we found that breathing skills training was slightly less effective than interoceptive exposure when each was added to cognitive restructuring (Craske, Rowe, Lewin, Noriega-Dimitri, 1997). Clearly, more dismantling research is needed.

Group formats appear to be as effective as individual treatment formats for CBT for panic and agoraphobia (Neron, Lacroix, & Chaput, 1995; Lidren et al., 1994<AQ: Reference entry needed>). One possible exception is that individual, one-to-one formats may be better in the long term with respect to symptoms of generalized anxiety and depression (Neron et al., 1995). However, more direct comparison between group and individual formats is warranted before firm conclusions can be made.

Most of the Panic Disorder treatment studies described in the previous sections averaged around 11 to 12 treatment sessions. Four to six sessions of PCT (Craske, Maidenberg, & Bystritsky, 1995; Roy-Byrne et al., 2005) seemed effective also, although the results were not as strong as those typically seen with 11 or 12 treatment sessions. On the other hand, another study demonstrated

equally effective results when delivering CBT for Panic Disorder across the standard 12 sessions versus approximately 6 sessions (Clark, Salkovskis, Hackmann, Wells, Ludgate, & Gelder, 1999), and a pilot study has indicated good effectiveness with intensive CBT over two days (Deacon & Abramowitz, 2006).

Self-directed treatments, with minimal direct therapist contact, are very beneficial to highly motivated and educated clients (e.g., Ghosh & Marks, 1987; Gould & Clum, 1995; Gould, Clum, & Shapiro, 1993). Computerized versions of CBT for Panic Disorder now exist. Computer-assisted and Internet versions of CBT are effective for Panic Disorder (e.g., Richards, Klein, & Carlbring, 2003). In one study, a 4-session computer-assisted CBT for Panic Disorder was less effective than a 12-session PCT at posttreatment, although they were equally effective at follow-up (Newman, Kenardy, Herman, & Taylor, 1997). However, findings from computerized programs for emotional disorders in general indicate that such treatments are more acceptable and successful when they are combined with therapist involvement (e.g., Carlbring, Ekselius, & Andersson, 2003).

Biological

Based on 19 placebo-controlled randomized clinical trials (Roy-Byrne & Cowley, 2002), SSRIs are the medication treatment of choice for Panic Disorder. Meta-analyses and reviews have reported medium to large effect sizes compared to placebo (e.g., Mitte, 2005; Bakker, van Balkom, & Spinhoven, 2002). The majority of trials have been short term, although several have examined and confirmed longer-term efficacy up to 1 year.

Benzodiazepines are effective agents for Panic Disorder as well. They work rapidly, within days to 1 week, and are even better tolerated than the very tolerable SSRI class of agents. However, they are limited by their risk of physiologic dependence and withdrawal, and the risk of abuse (Roy-Byrne & Cowley, 2002)

Numerous studies show clearly that discontinuation of medication results in relapse in a significant proportion of patients, with placebo-controlled discontinuation studies showing rates between 25% and 50% within 6 months, depending on study design (Roy-Byrne & Cowley, 2002). In addition, SSRIs, SNRIs, and benzodiazepines are associated with a time-limited withdrawal syndrome (considerably worse for the benzodiazepines), which itself may serve as an interoceptive stimulus that promotes or contributes to Panic Disorder relapse.

In terms of comparison between pharmacological and psychological approaches, a recent meta-analysis of 21 randomized trials involving over 1,700 patients with Panic Disorder With or Without Agoraphobia clearly showed the combined treatment with antidepressants and psychotherapy (behavior, CBT and "other") was superior to antidepressant alone and to psychotherapy alone in the

acute phase (Furukawa, Watanabe, & Churchill, 2006). After treatment discontinuation, combined treatment was superior to medication only but was not different from psychotherapy alone, and specifically CBT alone. Furthermore, following medication discontinuation, the combination of medication and CBT fared worse than CBT alone, suggesting the possibility that state- or context-dependent learning in the presence of medication may have attenuated the new learning that occurs during CBT.

Findings from the combination of fast-acting anxiolytics, especially the high-potency benzodiazepines, with behavioral treatments for Panic Disorder With Agoraphobia are contradictory (e.g., Marks et al., 1993; Wardle, Hayward, Higgitt, Stabl, Blizard, & Gray, 1994<AQ: Reference entry needed>). Nevertheless, several studies reliably show detrimental effects from chronic, naturalistic use of benzodiazepines on short-term and long-term outcome from cognitive-behavioral treatments for panic or agoraphobia (e.g., Fava et al., 2001; Otto, Pollack, & Sabatino, 1996; van Balkom, de Beurs, Koele, Lange, & van Dyck, 1996<AQ: Reference entry needed>; Westra, Stewart, & Conrad., 2002, for as- needed benzodiazepine use). Specifically, there is evidence for more attrition, poorer memory for CBT-related psychoeducation materials, poorer outcome, and greater relapse when cognitive-behavioral therapy is conducted in the context of the chronic, naturalistic use of benzodiazepines.

Prevention

Prevention for high-risk samples might not only halt the development of Panic Disorder but also ultimately prevent the development of other psychological disorders, since people who report panic attacks are at risk for other psychological problems including other anxiety disorders, depression, and substance abuse (e.g., Warren & Zgourides, 1988<AQ: Reference entry needed>). Moreover, comorbid diagnoses such as depressive disorders (e.g., Roy-Byrne, Stang, Wittchen, Ustun, et al., 2000<AQ: Reference entry needed>), and substance abuse (e.g., Marshall, 1997<AQ: Reference entry needed>) are believed to sometimes develop as a direct function of having Panic Disorder.

In addition, prevention using a brief cognitive-behavioral intervention is likely to be highly cost efficient. Cognitive-behavioral therapy is among the least expensive treatments for Panic Disorder (Gould, Otto, & Pollack, 1995). Prevention may cut indirect costs as well, given that people with Panic Disorder are heavy users of the medical system (e.g., Roy-Byrne et al., 1999). However, research on prevention is very limited.

Swinson, Soulios, Cox, and Kuch (1992)<AQ: Reference entry needed> briefly intervened with 33 patients who attended an emergency room with panic attacks. Within 24 hours of the panic attack, 17 were assigned to an exposure

condition and the remaining 16 were assigned to a reassurance condition. The latter were informed that what they had experienced was a panic attack, and that a panic attack is not dangerous. Participants in the exposure group were told the same reassuring information, and were advised that the most effective way to reduce fear is to confront the situation in which the panic attack occurred. One week later, the mean frequency of panic attacks decreased from 2.53 to .76 in the exposure group, but increased in the reassurance group from 2.50 to 3.38. This pattern was consistent over time, 3 months and 6 months later, and generalized to measures of anxiety (Swinson et al., 1992). Unfortunately, neither diagnostic evaluations nor independent assessments were conducted.

We (Gardenswartz & Craske, 2002conducted a selective/indicated prevention study that targeted Panic Disorder. College students were considered at risk for developing Panic Disorder if they reported at least one panic attack in the past year and had at least moderate anxiety sensitivity (as assessed by the Anxiety Sensitivity Index). Half of the participants (n=61) attended a 5-hour, group cognitive-behavioral workshop, modified from empirically supported cognitive-behavioral treatment for Panic Disorder (Barlow & Cerny, 1998). The other half was wait-listed. Six months later, 13.6% of the individuals in the control group developed Panic Disorder, as opposed to only 1.8% of individuals in the workshop group.

Summary and Future Directions

As the many studies discussed in this chapter attest, Panic Disorder enjoys the position as the most-researched anxiety disorder. The outgrowth of this intensive research includes an emerging understanding of the interplay between environmental and individual factors in shaping risk for Panic Disorder, converging evidence on the neurocircuitry of fear and panic, an integration of the latest advances in learning theory into models of etiology and maintenance, and the development of effective cognitive behavioral and pharmacological treatments. Nevertheless, despite a proliferation of studies and technological advances in methodology there remain areas in which the research is contradictory, including panic-related memory functioning and multiple areas of panic-related psychophysiology.

Looking toward the future, multiple new and continuing areas of investigation may attract increasing attention from researchers and clinicians alike. One rapidly expanding research area involves the role of genetics, and particularly the interaction of genetic and environmental factors, in increasing the risk for Panic Disorder. Future studies may range from investigating the interaction of specific genes with known environmental risk factors, to linking our emerging

understanding of parent and child interactions in the etiology and maintenance of anxiety disorders (e.g. Whaley, Pinto & Sigman, 1999; Moore, Whaley, & Sigman, 2004) with specific genetic risk factors (i.e., familial/environmental x individual x genetics interactions). New studies on genetics and environment interactions for anxiety disorders are emerging on a monthly basis, and although few currently focus specifically on Panic Disorder, more focused studies likely will emerge as the field expands. Additional potentially emerging areas include associations between in-utero, birth-related and early childhood trauma and genetics in increasing risk for Panic Disorder, as well as other forms of psychopathology.

On the treatment front, the role of experiential avoidance as a risk and maintenance factor for Panic Disorder has led to the development of a new line of acceptance-oriented behavioral treatments for anxiety disorders. One of the most prominent of the new therapies is Acceptance and Commitment Therapy (ACT; Hayes, Strosahl & Wilson, 1999). Eifert and Forsyth (2005) recently developed an ACT-based treatment manual for anxiety disorders, including Panic Disorder, and a randomized control trial is currently underway to test its efficacy. Whether ACT represents an improvement over traditional CBT therapies remains to be seen. Regardless, comparing ACT and traditional CBT presents an opportunity to examine the treatment process and outcome effects of mastery and control- versus acceptance-based strategies for Panic Disorder.

Acceptance and Commitment Therapy draws heavily on eastern-based mindfulness traditions.[4] Mindfulness meditation, in which mindfulness states are intentionally cultivated, forms the basis of an 8-week Mindfulness Based Stress Reduction (MBSR) program originally developed by Kabat-Zinn (1990) for patients with chronic pain. Since its initial application, MBSR has been applied to the treatment of Panic Disorder and Generalized Anxiety Disorder (Kabat-Zinn et al., 1992; Miller, Fletcher, & Kabat-Zinn, 1995), as well as an increasingly wide variety of psychological and medical conditions (e.g., Ramel, Goldin, Carmona & McQuaid, 2004; Robert-McComb, Tacon, Randolph & Caldera, 2004; Speca, Carolson, Goodey, & Angen, 2000). However, MBSR lacks randomized controlled trials for anxiety disorders, including Panic Disorder. Future research may see a proliferation of studies on ACT, MBSR, and other mindfulness and acceptance-oriented therapies for Panic Disorder (and other anxiety disorders), including much-needed randomized controlled trials. In addition, behavioral, physiological, and brain experimental studies investigating mechanisms by which mindfulness and acceptance effect attention, mood, and emotional regulation (e.g. Davidson et al., 2003; Eifert & Heffner, 2003; Broderick, 2005; Takahashi et al., 2005; Arch & Craske, 2006) are emerging. Finally, interest in experiential avoidance and mindfulness will likely spawn new self-report and behavioral measures to assess and validate these constructs; several such measures have

emerged already (e.g., Brown & Ryan, 2003; Hayes et al., 2004; Baer, Smith, Hopkins, Krietemeyer, & Toney, 2006).

With the emergence of new therapy treatments and the existence of proven, effective ones (e.g., CBT), it is important to consider that treatments are only as effective as the patients and clinicians who know about and use them. Despite the existence for over a decade of effective cognitive-behavioral treatments, a significant portion of individuals with Panic Disorder never receive CBT or any other form of treatment. In fact, many individuals with Panic Disorder are never treated by mental health professionals, but nearly 85% initially seek medical help for their symptoms (Katerndahl & Realini, 1995). Notably, Panic Disorder is not well recognized in medical settings (e.g., 80% nonrecognition in general medical patients referred for psychiatric evaluation, Roy-Byrne & Katon, 2000; 98%) not diagnosed in emergency departments, Fleet et al., 1997<AQ: Reference entry needed>) and is not well treated (e.g., Yelin et al., 1996<AQ: Reference entry needed>). Hence, panic researchers have begun adapting treatment models to the medical locations in which most (help-seeking) panic patients are seen: primary care and emergency room settings (Craske, Roy-Byrne, Stein, Donald-Sherbourne, Bystritsky, Katon, & Sullivan, 2002<AQ: Reference entry needed>). Adaptations that depart from traditional clinical trials include treatment in the medical setting rather than a mental health clinic and use of mental health trainees with minimal treatment experience or nonmental health professionals, such as primary care nurses, for conducting therapy and managing care. A recent multisite Panic Disorder treatment study conducted in a primary care setting demonstrated that an enhanced CBT and medication-based intervention was more effective across a number of outcome measures than usual care (Roy-Byrne, Craske, Stein, Sullivan et al., 2005), a finding that replicates an earlier medication-only study (Roy-Byrne, Katon, Cowley & Russo, 2002). Given the significant unmet needs of medical patients for recognition and treatment of Panic Disorder and the success of these early trials, future work in this direction is expected to continue.

Finally, given the enormous financial, quality of life, familial. and societal costs of Panic Disorder (e.g., Greenberg et al., 1999; Ettigi, Meyerhoff, Chirban, Jacob & Wilsons, 1997; Katerndahl & Realini, 1997), efforts toward early detection and prevention of panic disorder will continue to demand the attention of researchers, mental health professionals, and policymakers. Significant strides have been made in the identification of general risk and buffering factors in the development of anxiety disorders (see Zucker & Craske, 2001). Individuals at risk may be defined broadly (e.g., females, high neurotics, high stress) or more narrowly (e.g., children of parents with anxiety disorders, individuals with disorder-specific genetic profiles or high-anxiety sensitivity). Similarly, prevention and early detection efforts can be directly broadly through mass media or school-based programs, or more specifically, toward individuals at risk for anxiety disorders (selective prevention) or individuals with subclinical anxiety

symptoms (indicated prevention). Greater attention is currently needed to identify the most effective timing for prevention efforts, buffers that prevent high-risk or symptomatic individuals from developing full-blown anxiety disorders, and whether prevention efforts are better directed at broad vulnerability to anxiety or vulnerability to specific anxiety disorders (Zucker & Craske).

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Notes

1. Heart rate in humans is regulated by the sinoatrial node (SA), the natural pacemaker of the heart, located in the muscle fibers of the right atrial chamber. The SA is enervated by the sympathetic and parasympathetic branches of the autonomic nervous system, both of which modulate the regular rhythm set by the SA. The vagus, the 10th cranial nerve, serves as the principal source of parasympathetic communication between the SA and the central nervous system (Porges, 2003).

2. Few individuals in the sample met *DSM-IV* criteria for social phobia (n=1) or obsessive compulsive disorder (n=4; Kikuchi, 2005). Therefore, individuals with and without agoraphobia could not be compared on these anxiety disorders.

3. Specific phobias were not assessed, but by being most circumscribed, SPs would be hypothesized to load the least on negative affectivity.

4. Although scientifically defining the construct of mindfulness has been challenging (Bishop, 2002), it is thought to involve the cultivation of concentration, attention, and nonjudgmental acceptance toward whatever one is experiencing in the present moment (Bishop et al., 2004).