CHAPTER 1

Panic Disorder and Agoraphobia

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The treatment protocol described in this chapter represents one of the success stories in the development of evidence-based psychological treatments. Results from numerous studies indicate that this approach provides substantial advantages over placebo medication or alternative psychosocial approaches containing "common" factors, such as positive expectancies and helpful therapeutic alliances. In addition, this treatment forms an important part of every clinical practice guideline in either public health or other sources from countries around the world, describing effective treatments for panic disorder and agoraphobia. Results from numerous studies evaluating this treatment protocol, both individually and in combination with leading pharmacological approaches, suggest that this approach is equally effective as the best pharmacological approaches in the short term and more durable over the long term. But this treatment protocol has not stood still. For example, we have learned a great deal in recent years about neurobiological mechanisms of action in fear reduction, and the best psychological methods for effecting these changes and newly developed acceptance-based procedures have proven efficacious. In this chapter we present the latest version of this protocol, incorporating these changes and additions in the context of changes to diagnostic criteria in DSM-5, all as illustrated in a comprehensive account of the treatment of "Julie."—D. H. B.

Advances continue in the development of biopsychosocial models and cognitive-behavioral treatments for panic disorder and agoraphobia. The conceptualization of panic disorder as an acquired fear of certain bodily sensations, and agoraphobia as a behavioral response to the anticipation of related bodily sensations or their crescendo into a full-blown panic attack, continues to be supported by experimental, clinical, and longitudinal research. Furthermore, the efficacy of cognitive-behavioral treatments that target fear of bodily sensations and associated agoraphobic situations is well established. In addition to presenting an up-to-date review of treatment outcome data, this chapter covers recent theoretical and empirical developments in reference to etiological factors, the role of comorbid diagnoses in treatment, ways of optimizing learning during exposure therapy, and the effect of medication on cognitive-behavioral treatments. The chapter concludes with a detailed, session-by-session outline of cognitive-behavioral treatment for panic disorder and agoraphobia. This protocol has been developed in our clinics; the full protocol is detailed in available treatment manuals (Barlow & Craske, 2006; Craske & Barlow, 2006).
NATURE OF PANIC AND AGORAPHOBIA

Panic Attacks

“Panic attacks” are discrete episodes of intense fear or discomfort, accompanied by physical and cognitive symptoms, as listed in the DSM-5 panic attack checklist (American Psychiatric Association, 2013). Panic attacks are discrete by virtue of their sudden or abrupt onset and brief duration, as opposed to gradually building anxiety arousal. Panic attacks in panic disorder often have an unexpected quality, meaning that from the patient’s perspective, they appear to happen without an obvious trigger or at unexpected times. Indeed, the diagnosis of panic disorder is defined by recurrent “unexpected” panic attacks, followed by at least 1 month of persistent concern about their recurrence and their consequences, or by a significant change in behavior consequent to the attacks (American Psychiatric Association, 2013).

As with all basic emotions (Izard, 1992), panic attacks are associated with strong action tendencies: Most often, these are urges to escape, and less often, urges to fight. These fight and flight tendencies usually involve elevated autonomic nervous system arousal needed to support such fight-flight reactivity. Furthermore, perceptions of imminent threat or danger, such as death, loss of control, or social ridicule, often accompany such fight-flight reactivity. However, the features of urgency to escape, autonomic arousal, and perception of threat are not present in every self-reported occurrence of panic. For example, despite evidence for elevated heart rate or other indices of sympathetic nervous system activation during panic attacks on average (e.g., Wilkinson et al., 1998), Margraf, Taylor, Ehlers, Roth, and Agras (1987) found that 40% of self-reported panic attacks were not associated with accelerated heart rate. Moreover, in general, patients with panic disorder are more likely than nonanxious controls to report arrhythmic heart rate in the absence of actual arrhythmias (Barsky, Cleary, Sarnie, & Ruskin, 1994). Heightened anxiety about signs of autonomic arousal may lead patients to perceive cardiac events when none exist (Barlow, Brown, & Craske, 1994; Craske & Tsao, 1999). We believe that self-reported panic in the absence of heart rate acceleration or other indices of autonomic activation reflects anticipatory anxiety rather than true panic (Barlow et al., 1994), especially because more severe panic attacks are more consistently associated with accelerated heart rate (Margraf et al., 1987). Sometimes individuals report intense abrupt fear in the absence of perceptions of threat or danger. This has been termed “noncognitive” panic (Rachman, Lopata, & Levitt, 1988; see Kirmayer, Craske, Epsttein, & Whitehouse, 2009). Finally, the urgency to escape is sometimes weakened by situational demands for continued approach and endurance, such as performance expectations or job demands, thus creating discordance between behavioral responses on the one hand, and verbal or physiological fear responses on the other.

A subset of individuals with panic disorder 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 during wakeful states (Craske & Barlow, 1989; Uhe, 1994). Nocturnal panic does not refer to waking from sleep and panicking after a lapse of waking time, or nighttime arousals induced by nightmares or environmental stimuli (e.g., unexpected noises). Instead, nocturnal panic is an abrupt waking from sleep in a state of panic, without an obvious trigger. Nocturnal panic attacks reportedly most often occur between 1 and 3 hours after sleep onset, and only occasionally more than once per night (Craske & Barlow, 1989). Surveys of select clinical groups suggest that nocturnal panic is relatively common among individuals with panic disorder: 44–71% report having experienced nocturnal panic at least once, and 30–45% report repeated nocturnal panic (Craske & Barlow, 1989; Krystal, Woods, Hill, & Charney, 1991; Mellman & Uhe, 1989; Roy-Byrne, Mellman, & Uhe, 1988; Uhe, 1994). Individuals who suffer frequent nocturnal panic often become fearful of sleep and attempt to delay sleep onset. Avoidance of sleep may result in chronic sleep deprivation, which in turn precipitates more nocturnal panic (Uhe, 1994).

“Nonclinical” panic attacks occur occasionally in approximately 3–5% of people in the general population who do not otherwise meet criteria for panic disorder (Norton, Cox, & Malan, 1992). Also, panic attacks occur across a variety of anxiety and mood disorders (Barlow et al., 1985), as well as substance use, personality disorders and psychoses (Craske et al., 2010) and are not limited to panic disorder. Indeed, the ubiquity of panic attacks has been emphasized in DSM-5 (American Psychiatric Association, 2013) where panic attacks are designated as a potential specifier for any DSM disorder. As stated earlier, the defining feature of panic disorder is not the presence of panic attacks per se, but involves additional anxiety about the recurrence of panic or its consequences, or a significant behavioral change be anxiety ations in th person wi cal panic person wi to panic. point.

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change because of the panic attacks. It is the additional anxiety about panic combined with catastrophic cognitions in the face of panic that differentiate between the person with panic disorder and the occasional nonclinical panicer (e.g., Tolin, Lucas, & Nelson, 1999) or the person with other anxiety disorders who also happens to panic. The following scenario exemplifies the latter point.

**PATIENT:** Sometimes I lay awake at night thinking about a million different things. I think about what is going to happen to my daughter if I get sick. Who will look after her, or what would happen if my husband died and we didn’t have enough money to give my daughter a good education? Then I think about where we would live and how we would cope. Sometimes I can work myself up so much that my heart starts to race, my hands get sweaty, and I feel dizzy and scared. So I have to stop myself from thinking about all those things. I usually get out of bed and turn on the TV—anything to get my mind off the worries.

**THERAPIST:** Do you worry about the feelings of a racing heart, sweating, and dizziness happening again?

**PATIENT:** No. They’re unpleasant, but they are the least of my concerns. I am more worried about my daughter and our future.

This scenario illustrates the experience of panic that is not the central focus of the person’s anxiety. More likely, this woman has generalized anxiety disorder, and her uncontrollable worry leads her to panic on occasion. The next example is someone with social anxiety disorder, who becomes very concerned about panicking in social situations, because the possibility of a panic attack increases her concerns about being judged negatively by others.

**PATIENT:** I am terrified of having a panic attack in meetings at work. I dread the thought of others noticing how anxious I am. They must be able to see my hands shaking, the sweat on my forehead, and worst of all, my face turning red.

**THERAPIST:** What worries you most about others noticing your physical symptoms?

**PATIENT:** That they will think that I am weird or strange.

**THERAPIST:** Would you be anxious in the meetings if the panic attacks were gone?

**PATIENT:** I would still be worried about doing or saying the wrong thing. It is not just the panic attacks that worry me.

**THERAPIST:** Are you worried about panic attacks in any other situations?

**PATIENT:** Formal social events and sometimes when I meet someone for the first time.

In this case, even though the patient experiences panic attacks, the real concern is about being judged negatively by others consequent to panic attacks, and the panic attacks do not occur in situations other than social ones. Hence, this presentation is most aptly described as social anxiety.

**Agoraphobia**

“Agoraphobia” refers to avoidance or encumbrance with dread of situations from which escape might be difficult or help is unavailable in the event of a panic-like symptoms (including but not limited to panic attacks) or other incapacitating symptoms, such as loss of bowel control or vomiting, disorientation (especially in children), or sense of falling (especially in older adults) (American Psychiatric Association, 2013). Typical agoraphobic situations include shopping malls, waiting in line, movie theaters, traveling by car or bus, crowded restaurants, and being alone. “Mild” agoraphobia is exemplified by the person who hesitates about driving long distances alone but manages to drive to and from work, prefers to sit on the aisle at movie theaters but still goes to movies, and avoids crowded places. “Moderate” agoraphobia is exemplified by the person whose driving is limited to a 10-mile radius from home and only if accompanied, who shops at off-peak times and avoids large supermarkets, and who avoids flying or traveling by train. “Severe” agoraphobia refers to very limited mobility, sometimes even to the point of becoming housebound.

**Relationship between Panic and Agoraphobia**

The relationship between panic and agoraphobia is complex. On the one hand, not all persons who panic develop agoraphobia, and the extent of agoraphobia that emerges is highly variable (Craske & Barlow, 1988). Various factors have been investigated as potential predictors of agoraphobia. Although agoraphobia tends to increase as history of panic lengthens, a significant
proportion of individuals panic for many years without developing agoraphobic limitations. Nor is agoraphobia related to age of onset or frequency of panic (Cox, Endler, & Swinson, 1995; Craske & Barlow, 1988; Kikuchi et al., 2005; Rapee & Murrill, 1988). Some studies report more intense physical symptoms during panic attacks when there is more agoraphobia (e.g., de Jong & Bouman, 1995; Goisman et al., 1994; Noyes, Clancy, Garvey, & Anderson, 1987; Telch, Brouillard, Telch, Agras, & Taylor, 1989). Others fail to find such differences (e.g., Cox et al., 1995; Craske, Miller, Rotunda, & Barlow, 1990). On the one hand, fears of dying, going crazy, or losing control do not relate to level of agoraphobia (Cox et al., 1995; Craske, Rapee, & Barlow, 1988). On the other hand, concerns about social consequences of panic may be stronger when there is more agoraphobia (Amiriling et al., 1997; de Jong & Bouman, 1995; Rapee & Murrill, 1988; Telch, Brouillard, et al., 1989). In addition, Kikuchi and colleagues (2005) found that individuals who develop agoraphobia within 6 months of the onset of panic disorder have a higher prevalence of generalized anxiety disorder but not major depression. However, whether social evaluation concerns or comorbidity are precursors or are secondary to agoraphobia remains to be determined. Occupational status also predicts agoraphobia, accounting for 18% of the variance in one study (de Jong & Bouman, 1995). Perhaps the strongest predictor of agoraphobia is sex; the ratio of males to females shifts dramatically in the direction of female predominance as level of agoraphobia worsens (e.g., Thyer, Himle, Curtis, Cameron, & Nesse, 1985).

On the other hand, not everyone with panic disorder has a history of panic attacks or even panic-like symptoms, although a history of panic is much more common in treatment-seeking samples of individuals with agoraphobia than in epidemiological samples (Wittchen, Gloster, Beesdo-Baum, Fava, & Craske, 2010). Nonetheless, the prevalence of agoraphobia with a history of panic disorder, panic attacks, or panic-like symptoms was reported to be as high as the combined rates of panic disorder with and without agoraphobia across all epidemiological studies (Wittchen et al., 2010). Approximately 50% of individuals from community samples who endorse agoraphobia do not endorse panic attacks. Furthermore, agoraphobia without panic-like features appears to be as impairing as panic disorder without agoraphobia, although the combination is usually associated with even more impairment. In addition, some differences exist between them in terms of incidence, comorbidity, and response to treatment (Wittchen et al., 2010). For these reasons, panic disorder and agoraphobia are now recognized as two distinct, albeit highly comorbid, disorders in DSM-5 (American Psychiatric Association, 2013).

**PRESENTING FEATURES**

From the latest epidemiological study, the National Comorbidity Survey Replication (NCS-R; Kessler, Berglund, Demler, Jin, & Walters, 2005; Kessler, Chiu, Demler, & Walters, 2005) 12-month prevalence estimates for panic disorder are approximately 2% in adults and adolescents. Lower estimates have been reported for some Asian, African and Latin American countries, ranging from 0.1 to 0.8% (Lewis-Fernandez et al., 2010). The 12-month rates for agoraphobia are approximately 1.7%, and the lifetime morbidity risk is 3.7% (Kessler et al., 2012).

The modal age of onset for panic disorder is late teenage years and early adulthood (Kessler, Berglund, et al., 2005). In fact, although panic disorder is rare below the age of 14, a substantial proportion of adolescents report panic attacks (e.g., Hayward et al., 1992), and panic disorder in children and adolescents tends to be chronic and comorbid with other anxiety, mood, and disruptive disorders (Biederman, Faraone, M RR, & Moore, 1997). Treatment is usually sought much later, around age 34 (e.g., Noyes et al., 1986). Similarly, agoraphobia may occur in childhood but the incidence peaks in late adolescence and early adulthood (Beesdo, Knapp, & Pine, 2007; Bittner et al., 2007); the mean age of onset is 17 years (Kessler et al., 2012), and older in the absence of history of panic disorder or panic attacks. Rates of panic disorder decline in older adults, possibly diminishing to subclinical levels (Wolitzky-Taylor, Castriotti, Lenze, Stanley, & Craske, 2010). Similarly, 12-month prevalence rates for agoraphobia reduce to 0.4% in individuals over the age of 65 years (Kessler et al., 2006). The overall ratio of females to males is approximately 2:1 (Kessler et al., 2006) and, as mentioned already, the ratio shifts dramatically in the direction of female predominance as level of agoraphobia worsens (e.g., Thyer et al., 1985).

Rarely do the diagnoses of panic disorder or 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., Brown,
Campbell, Lehman, Grishman, & Mancill, 2001; Goeisman, Goldenberg, Vasile, & Keller, 1995; Kessler, Chiu, et al., 2005). Also, 25–60% of persons with panic disorder also meet criteria for a personality disorder, mostly avoidant and dependent personality disorders (e.g., Chambless & Renneberg, 1988). However, the nature of the relationship with personality disorders remains unclear. For example, comorbidity rates are highly dependent on the method used to establish Axis II diagnosis, as well as the co-occurrence of depressed mood (Alens & Torgersen, 1990; Chambless & Renneberg, 1988). Moreover, the fact that abnormal personality traits improve and some “personality disorders” even remit after successful treatment of panic disorder (Black, Monahan, Wesner, Gabel, & Bowers, 1996; Mavissakalian & Hamman, 1987; Naves, Reich, Suedzer, & Christiansen, 1991) raises questions about the validity of Axis II diagnoses. The issue of comorbidity with personality disorders and its effect on treatment for panic disorder and agoraphobia is described in more detail in a later section.

Finally, panic disorder and agoraphobia tend to be chronic conditions, with severe financial and interpersonal costs (Wittechen et al., 2010). Only a minority of untreated individuals remit without subsequent relapse within a few years if not treated (Emmelkamp & Wittechen, 2009; Katachig & Amering, 1998; Roy-Byrne & Cowley, 1995). Also, individuals with panic disorder overutilize medical resources compared to the general public and individuals with other “psychiatric” disorders (e.g., Katon et al., 1990; Roy-Byrne et al., 1999).

**History of Psychological Treatment for Panic Disorder and Agoraphobia**

It was not until the publication of DSM-III (American Psychiatric Association, 1980) that panic disorder with or without agoraphobia was recognized as a distinct anxiety problem. Until that time, panic attacks were viewed primarily as a form of free-floating anxiety. Consequently, psychological treatment approaches were relatively nonspecific. They included relaxation and cognitive restructuring for stressful life events in general (e.g., Barlow, O'Brien, & Last, 1984). Many presumed that pharmacotherapy was necessary for the control of panic. In contrast, the treatment of agoraphobia was quite specific from the 1970s onward, with primarily exposure-based approaches to target fear and avoidance of specific situations. However, relatively little consideration was given to panic attacks in either the conceptualization or treatment of agoraphobia. The development of specific panic control treatments in the middle to late 1980s shifted interest away from agoraphobia. Interest in agoraphobia was subsequently renewed, specifically in terms of whether panic control treatments are sufficient for the management of agoraphobia, and whether their combination with treatments that directly target agoraphobia is superior overall. We address these questions in more detail after describing the conceptualization that underlies cognitive-behavioral approaches to the treatment of panic and agoraphobia.

**Conceptualization of Etiological and Maintaining Factors for Panic Disorder and Agoraphobia**

Several independent lines of research (Barlow, 1988; Clark, 1986; Ehlers & Mergraf, 1989) converged in the 1980s on the same basic conceptualization of panic disorder as an acquired fear of bodily sensations, particularly sensations associated with autonomic arousal. Psychological and biological predispositions are believed to enhance the vulnerability to acquire such fear. These interacting vulnerabilities have been organized into an etiological conception of anxiety disorders in general, referred to as “triple vulnerability theory” (Barlow, 1988, 2002; Suárez, Bennett, Goldstein, & Barlow, 2008). First, genetic contributions to the development of anxiety and negative affect constitute a generalized (heritable) biological vulnerability. Second, evidence supports a generalized psychological vulnerability to experience anxiety and related negative affective states, characterized by a diminished sense of control arising from early developmental experiences. Although the unfortunate co-occurrence of generalized biological and psychological vulnerabilities may be sufficient to produce anxiety and related states, particularly generalized anxiety disorder and depression, a third vulnerability seems necessary to account for the development of at least some specific anxiety disorders, including panic disorder: that is, early learning experiences in some instances seem to focus anxiety on particular areas of concern. In panic disorder, the experience of certain somatic sensations becomes associated with a heightened sense of threat and danger. This specific psychological vulnerability, when coordi-
nated with the generalized biological and psychological vulnerabilities mentioned earlier, seems to contribute to the development of panic disorder. Fear conditioning, avoidant responding, and information-processing biases are believed to perpetuate such fear. It is the perpetuating factors that are targeted in the cognitive-behavioral treatment approach. What follows is a very brief review of some contributory factors with practical relevance for panic disorder.

**Vulnerability Factors**

**Genetics and Temperament**

The temperament most associated with anxiety disorders, including panic disorder, is neuroticism (Eysenck, 1967; Gray, 1982), or proneness to experience negative emotions in response to stressors. A closely linked construct, “negative affectivity,” is the tendency to experience a variety 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 individuals with each anxiety disorder (and depression) from controls with no mental disorder. Lower-order factors discriminate among anxiety disorders, with “fear of fear” being the factor that discriminates panic disorder from other anxiety disorders (Brown, Chorpita, & Barlow, 1998; Prenoveau et al., 2010; Zinbarg & Barlow, 1996). 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). However, these findings derive from cross-sectional datasets.

Longitudinal prospective evidence for the role of neuroticism in predicting the onset of panic disorder is relatively limited. Specifically, neuroticism predicted the onset of panic attacks in adolescents (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 comprehensively evaluating the role of neuroticism in the prediction of subsequent panic disorder.

Numerous multivariate genetic analyses of human twin samples consistently attribute approximately 30-50% of variance in neuroticism to additive genetic factors (Eley, 2001; Lake, Eaves, Maes, Heath, & Martin, 2003). In addition, anxiety and depression appear to be variable expressions of the heritable tendency toward neuroticism (Kendler, Heath, Martin, & Eaves, 1987). Symptoms of panic (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., 1987) and neuroticism (Martin, Jardine, Andrews, & Heath, 1988).

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) and chromosome 9 (Thorgeirsson et al., 2003), but the exact genes remain unknown. Findings regarding markers for the cholecystokinin-B receptor gene have been inconsistent (cf. Hamilton et al., 2001; van Megen, Westenberg, den Boer, & Kahn, 1996). Also, association and linkage studies implicate the adenosine receptor gene in panic disorder (Deckert et al., 1998; Hamilton et al., 2004). An allele of the neuropeptide S receptor gene on chromosome 7 was linked in a male-specific manner to panic disorder and not to schizophrenia or attention deficit disorder (Okamura et al., 2011), whereas the same gene was linked in a female-specific manner to panic disorder compared to healthy controls (Domschke et al., 2011). Thus, at this stage, the results are rather piecemeal and sometimes inconsistent, and there is no evidence at this point for a specific link between genetic markers and temperament, on the one hand, and panic disorder on the other. Rather, neurobiological factors seem to comprise a nonspecific vulnerability.

**Anxiety Sensitivity**

As described earlier, neuroticism is viewed as a higher-order factor characteristic of all anxiety disorders, with “fear of fear” being more unique to panic disorder. The construct “fear of fear” overlaps with the construct “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 of the Anxiety Sensitivity Index (Zinbarg & Barlow, 1996; Zinbarg,
Barlow, & Brown, 1997). Therefore, beliefs that physical symptoms of anxiety are harmful seem to be particularly relevant to panic disorder and may comprise a specific psychological vulnerability.

Anxiety sensitivity is presumed to confer a risk factor for panic disorder because it primes fear reactivity to bodily sensations. In support, anxiety sensitivity predicts subjective distress and reported symptomatology in response to procedures that induce strong physical sensations, such as CO₂ inhalation (Forsyth, Palau, & Duff, 1999), balloon inflation (Messenger & Shean, 1998), and hyperventilation (Sturges, Goetsch, Ridley, & Whittal, 1998) in nonclinical samples, even after researchers control 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 et al., 2000), college students (Maller & Reiss, 1992), and community samples with specific phobias or no anxiety disorders (Ehlers, 1995). The predictive relationship remains after researchers control for prior depression (Hayward et al., 2000). In addition, Anxiety Sensitivity Index scores predicted spontaneous panic attacks and worry about panic (and anxiety more generally), during an acute military stressor (i.e., 5 weeks of basic training), even after researchers control for history of panic attacks and trait anxiety (Schmidt et al., 1997, 1999).

Finally, panic attacks themselves elevate anxiety sensitivity over a 5-week period in adults (Schmidt et al., 1999), and over a 1-year period in adolescents, albeit to a lesser extent (Weems, Hayward, Killen, & Taylor, 2002).

However, Bouton, Mineka, and Barlow (2001) have noted that the relationship between anxiety sensitivity and panic attacks in these studies is relatively small, not exclusive to panic, and weaker than the relationship between panic and neuroticism. Furthermore, these studies have evaluated panic attacks and worry about panic but not the prediction of diagnosed panic disorder. Thus, the causal significance of anxiety sensitivity for panic disorder remains to be fully understood.

**History of Medical Illness and Abuse**

Other studies highlight the role of medical illnesses as contributing to a specific psychological vulnerability for panic disorder. For example, using the Dunedin Multidisciplinary Study database, we found that experience with personal respiratory disturbance (and parental poor health) as a youth predicted panic disorder at age 18 or 21 (Craske et al., 2001). This finding is consistent with reports of more respiratory disturbance in the history of patients with panic disorder compared to other patients with anxiety disorders (Verburg, Griez, Meijer, & Pols, 1995). Furthermore, first-degree relatives of patients with panic disorder had a significantly higher prevalence of chronic obstructive respiratory disease, asthma in particular, than first-degree relatives of patients with other anxiety disorders (van Beek, Schuurs, & Friez, 2005).

Childhood experiences of sexual and physical abuse may also prime panic disorder. Retrospective reports of such childhood abuse were associated with panic disorder onset at ages 16–21 years in a longitudinal analysis of New Zealanders from birth to age 21 (Goodwin, Ferguson, & Horwood, 2005). This finding is consistent with multiple cross-sectional studies in both clinical and community samples (e.g., Bandelow et al., 2002; Kendler et al., 2000; Kessler, Davis, & Kendler, 1997; Moisan & Engels, 1995; Stein et al., 1996). The association with childhood abuse is stronger for panic disorder than for other anxiety disorders, such as social phobia (Soifer, Gershuny, Marzol, Cito, & Pollack, 2002; Stein et al., 1996) and obsessive-compulsive disorder (Stein et al., 1996). In addition, some studies report an association between panic disorder and exposure to violence between other family members, generally interpersonal violence (e.g., Bandelow et al., 2002; Moisan & Engels, 1995), whereas another study did not (Goodwin et al., 2005). Retrospective reporting of childhood abuse and familial violence in all of these studies, however, limits the findings.

**Interceptive Awareness**

Patients with panic disorder, as well as nonclinical panicizers, appear to have heightened awareness of, or ability to detect, bodily sensations of arousal (e.g., Ehlers & Breuer, 1992; 1996; Ehlers, Breuer, Dohn, & Feigenbaum, 1995; Zoellner & Craske, 1999). Discrepancy findings (e.g., Antony et al., 1995; Rapee, 1994) exist but have been attributed to methodological artifact (Ehlers & Breuer, 1996). Ability to perceive heartbeat, in particular, appears to be a relatively stable individual-difference variable given that it does not differ between untreated and treated patients with panic disorder (Ehlers & Breuer, 1992), or from before to after successful treatment (Antony, Meadows, Brown, & Barlow, 1994; Ehlers et al., 1995). Thus, interceptive accuracy may be a predisposing trait for panic disorder that increases the probability of perceiving sensa-
tions that in turn may trigger a panic attack. Whether interoceptive awareness is learned, and represents another specific psychological vulnerability, or is more dispositional remains to be determined.

Separate from interoception is the issue of propensity for intense autonomic activation. As noted earlier, some evidence points to a unique genetic influence on the reported experience of breathlessness, heart pounding, and a sense of terror (Kendler et al., 1987). Conceivably, cardiovascular reactivity presents a unique physiological predisposition for panic disorder. In support of this, cardiac symptoms and shortness of breath predict later development of panic attacks and panic disorder (Keyl & Eaton, 1990). Unfortunately, these data derive from report of symptoms, which is not a good index of actual autonomic state (Pennebaker & Roberts, 1992) and may instead reflect interoception.

**Initial Panic Attacks**

From an evolutionary standpoint, fear is a natural and adaptive response to threatening stimuli. However, the fear experienced during the first unexpected panic attack is often unjustified due to the lack of an identifiable trigger or antecedent; hence, it represents a “false alarm” (Barlow, 1988; 2002). The large majority of initial panic attacks are recalled as occurring outside of the home, while driving, walking, at work, or at school (Craske et al., 1990), generally in public (Lelliott, Marks, McNamee, & Tobena, 1989), and on a bus, plane, subway, or in social-evaluative situations (Shulman, Cox, Swinson, Kuch, & Reichman, 1994). Barlow (1988) and Craske and Rowe (1997b) believe situations that set the scene for initial panic attacks are ones in which bodily sensations are perceived as the most threat because of impairment of functioning (e.g., driving), entrapment (e.g., air travel, elevators), negative social evaluation (e.g., job, formal social events), or distance from safety (e.g., unfamiliar locales). Entrapment concerns may be particularly salient for the subsequent development of agoraphobia (Faravelli, Biondi, Paterniti, & Scarpati, 1992).

**Maintenance Factors**

Acute “fear of fear” (or, more accurately, anxiety focused on somatic sensations) that develops after initial panic attacks in vulnerable individuals refers to anxiety about certain bodily sensations associated with panic attacks (e.g., racing heart, dizziness, paresthesias) (Barlow, 1988; Goldstein & Chambless, 1978) and is attributed to two factors. The first is interoceptive conditioning, or conditional fear of internal cues, such as elevated heart rate, because of their association with intense fear, pain, or distress (Razran, 1961). Specifically, interoceptive conditioning refers to low-level somatic sensations of arousal or anxiety becoming conditional stimuli, so that early somatic components of the anxiety response come to elicit significant bursts of anxiety or panic (Bouton et al., 2001). An extensive body of experimental literature attests to the robustness of interoceptive conditioning (e.g., Dworkin & Dworkin, 1999), particularly with regard to early interoceptive drug-onset cues becoming conditional stimuli for larger drug effects (e.g., Sokołowska, Siegel, & Kim, 2002). In addition, interoceptive conditional responses are not dependent on conscious awareness of triggering cues (Razran, 1961); thus, they have been observed in patients under anesthesia (e.g., Block, Ghoneim, Fowles, Kumar, & Pathak, 1987). Within this model, then, slight changes in relevant bodily functions that are not consciously recognized may elicit conditional anxiety or fear and panic due to previous pairings with panic (Barlow, 1988; Bouton et al., 2001); the result would be an unexpected panic attack. Further support for a conditioning model comes from evidence that individuals with panic disorder, as well as other anxiety disorders, show elevated fear conditioning and weakened fear extinction in laboratory paradigms (Lissek et al., 2005), suggesting that they are more prone to developing fear through negative associations, and once acquired, their fear is less likely to diminish with time. This pattern seems to be compounded for individuals with panic disorder who additionally show impaired safety learning (Lissek et al., 2009) and greater fear generalization (Lissek et al., 2010) in laboratory paradigms. In other words, once fear of specific bodily sensations is acquired, individuals with panic disorder may have difficulty perceiving other sensations as being harmless and may be more likely to generalize their fear to various bodily states.

The second factor, offered by Clark (1986) to explain acute fear of panic-related body sensations, is catastrophic misappraisals of bodily sensations (misinterpretation of sensations as signs of imminent death, loss of control, etc.). We have taken issue with the purely cognitive model of panic disorder by stating that it cannot account for panic attacks devoid of conscious cognitive appraisal without turning to constructs such as “automatic appraisals,” which prove to be unstable.
Panic Disorder and Agoraphobia

(Bouton et al., 2001). Catastrophic misappraisals may accompany panic attacks because they are a natural part of the constellation of responses that go with panic, or because they have been encouraged and reinforced much like sick role behaviors during childhood. In addition, such thoughts may become conditioned stimuli that trigger anxiety and panic, as demonstrated via panic induction through presentation of pairs of words involving sensations and catastrophic outcomes (Clark et al., 1988). In this case, catastrophic cognitions may well be sufficient to elicit conditioned panic attacks, but not necessary.

Whether cognitively or noncognitively based, excessive anxiety over panic-related bodily sensations in panic disorder is well supported. Persons with panic disorder endorse strong beliefs that bodily sensations associated with panic attacks cause physical or mental harm (e.g., Chambless, Caputo, Bright, & Gullagher, 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 “fatalities” (e.g., Ehlers, Margraf, Davies, & Roth, 1988; Hope, Rapee, Heimberg, & Dombeck, 1990); catastrophic words, such as “death” and “insane” (e.g., Maidenberg, Chen, Craske, Bohn, & Byrutsisky, 1996; McNally, Riemann, Louro, Lutkach, & Kim, 1992); and heartbeat stimuli (Kroeze & van der Hout, 2000); however, attentional bias is not always found; e.g., DeCort, Hermans, Spruyt, Griez, & Schuurs, 2008). Also, individuals with panic disorder show enhanced brain potentials in response to panic-related words (Paul, Amthor, Mullberger, Daniel, & Wiedemann, 2005). In addition, they are more likely to become anxious in procedures that elicit bodily sensations similar to those experienced during panic attacks, including benign cardiovascular, respiratory, and audiovestibular exercises (Antony, Ledley, Liss, & Swinson, 2006; Jacob, Purman, Clark, & Durrant, 1992), as well as more invasive procedures, such as CO₂ inhalations, compared to patients with other anxiety disorders (e.g., Perna, Bertani, Arancia, Ronchi, & Bellodi, 1995; Rapee, 1986; Rapee, Brown, Antony, & Barlow, 1992) or healthy controls (e.g., Gorman et al., 1994). The findings are not fully consistent, however, because patients with panic disorder did not differ from patients with social phobia in response to an epinephrine challenge (Volman, van Zijlverd, Tilders, & van Dyck, 1996). Nonetheless, individuals with panic disorder also fear signals that ostensibly reflect heightened arousal and false physiological feedback (Craske & Freed, 1995; Craske, Lang, et al., 2002; Ehlers, Margraf, Roth, Taylor, & Birnbaum, 1988).

Distress over bodily sensations is likely to generate ongoing distress for a number of reasons. First, in the immediate sense, autonomic arousal generated by fear in turn intensifies the feared sensations, thus creating a reciprocating cycle of fear and sensations that is sustained until autonomic arousal abates or the individual perceives safety. Second, because bodily sensations that trigger panic attacks are not always immediately obvious, they may generate the perception of unexpected or “out of the blue” panic attacks (Barlow, 1988) that causes even further distress (Craske, Glover, & DeCala, 1995). Third, the perceived uncontrollability, or inability to escape or terminate bodily sensations, again, is likely to generate heightened anxiety (e.g., Mulier, Lademansler, & Ryan, 1985; Mineka, Cook, & Miller, 1984). Unpredictability and uncontrollability, then, are seen as enhancing general levels of anxiety about “When is it going to happen again?” and “What do I do when it happens?” thereby contributing to high levels of chronic anxious apprehension (Barlow, 1988, 2002). In turn, anxious apprehension increases the likelihood of panic by directly increasing the availability of sensations that have become conditioned cues for panic and/or attentional vigilance for these bodily cues. Thus, a maintaining cycle of panic and anxious apprehension develops. Also, subtle avoidance behaviors are believed to maintain negative beliefs about feared bodily sensations (Clark & Ehlers, 1993). Examples include holding onto objects or persons for fear of fainting, sitting and remaining still for fear of a heart attack, and moving slowly or searching for an escape route because one fears acting foolish (Salkovskis, Clark, & Gelder, 1996). Such avoidance includes “experiential avoidance,” or being unwilling to remain in contact with particular private experiences, in this case bodily sensations and catastrophic cognitions. Experiential avoidance is believed to contribute to overall distress and dysfunction in general (Hayes et al., 1996), and appears to correlate with panic-related worries and disability in individuals with panic disorder (Kampf et al., 2012). Further support for the role of experiential avoidance comes from evidence for instructors to accept symptoms of panic to result in less fear and avoidance in patients with panic disorder (Campbell-Sills, Barlow, Brown, & Hofmann, 2006; Ebert & Hefner, 2003), including CO₂ inhalation challenges (Levitt, Brown, Orsillo, & Barlow, 2004). Finally, anxiety may develop
over specific contexts in which the occurrence of panic would be particularly troubling (i.e., situations associated with impairment, entrapment, negative social evaluation, and distance from safety). These anxieties may contribute to agoraphobia, which in turn maintains distress by preventing disconfirmation of catastrophic misappraisals and extinction of conditioned responding. Clearly, this model targets panic disorder and agoraphobia, and is not as relevant to agoraphobia in the absence of panic attacks or panic-like symptoms.

**TREATMENT VARIABLES**

**Setting**

There are several different settings for conducting cognitive-behavioral therapy for panic disorder and agoraphobia. The first, the outpatient clinic-office setting, is suited to psychoeducation, cognitive restructuring, assignment, and feedback regarding homework assignments and role-play rehearsals. In addition, certain exposures can be conducted in the office setting, such as interoceptive exposure to feared bodily sensations we describe later. Outpatient settings have extended from mental health settings to primary care settings (e.g., Craske, Roy-Byrne, et al., 2002; Craske et al., 2011; Roy-Byrne, Craske, et al., 2005; Roy-Byrne et al., 2010; Sharp, Power, Simpson, Swanson, & Anstee, 1997). This extension is particularly important because of the higher prevalence of panic disorder in primary care settings (e.g., Shear & Schulberg, 1995; Tiemens, Ormel, & Simon, 1996). However, whether a mental health or a primary care office is being used, the built-in safety signals of such an office may limit the generalizability of learning that takes place in that setting. For example, learning to be less afraid in the presence of the therapist, or in an office located near a medical center, may not necessarily generalize to conditions in which the therapist is not present, or when the perceived safety of a medical center is not close by. For this reason, homework assignments to practice cognitive-behavioral skills in a variety of different settings are particularly important.

In the second setting, the natural environment, cognitive restructuring and other anxiety management skills are put into practice as the patient faces feared situations. The latter is called *in vivo* exposure and can be conducted with the aid of the therapist or alone. Therapist-directed exposure is particularly useful for patients who lack a social network to support *in vivo* exposure assignments, and more valuable than self-directed exposure for patients with more severe agoraphobia (Holden, O'Brien, Barlow, Stetson, & Infante, 1983). Therapist-directed exposure is essential to "guided mastery exposure," in which the therapist gives corrective feedback about the way the patient faces feared situations to minimize unnecessary defensive behaviors. For example, patients are taught to drive in a relaxed position and to walk across a bridge without holding the rail. On the one hand, guided mastery exposure has been shown to be more effective than "stimulus exposure" when patients attempt simply to endure the situation alone until fear subsides, without the benefit of ongoing therapist feedback (Williams & Zane, 1989). On the other hand, self-directed exposure is very valuable also, especially to the degree that it encourages independence and generalization of the skills learned in treatment to conditions in which the therapist is not present. Thus, the most beneficial approach in the natural environment is to proceed from therapist-directed to self-directed exposure.

In telephone-guided treatment, an interesting variation that combines the office and the natural environment, therapists direct patients with agoraphobia by phone to conduct *in vivo* exposure to feared situations (NeNamee, O'Sullivan, Lelliot, & Marks, 1989; Swanson, Fergus, Cox, & Wickwire, 1995) or provide instruction in panic control skills (Cote, Gauthier, Laberge, Cormier, & Plamondon, 1994). In addition, one small study showed that cognitive-behavioral therapy was as effective when delivered by videoconference as in person (Bouchard et al., 2004).

Self-directed treatments, with minimal direct therapist contact, take place in the natural environment and are beneficial for highly motivated and educated patients (e.g., Ghosh & Marks, 1987; Gould & Clum, 1995; Gould, Clum, & Shapiro, 1993; Lidren et al., 1994; Schneider, Mataix-Cols, Marks, & Bachofen, 2005). On the other hand, self-directed treatments are less effective for more severely affected patients (Holden, O'Brien, Barlow, Stetson, & Infante, 1983); for those with more comorbidity (Hecker, Losee, Rehbock-Nay, & Maki, 2004), less motivation, and less education; or for patients who are referred as opposed to recruited through advertisement (Hecker, Losee, Fritsler, & Fink, 1996). Self-directed treatments have expanded beyond workbooks and manuals to computerized and Internet versions (e.g., Carlbring, Ekselius, & Andersson, 2003; Richards, Klein, & Aus-
tin, 2006; Richards, Klein, & Carlin, 2003). In general, these treatments yield very positive results with strong effect sizes (Andrews, Cuijpers, Craske, McEvoy, & Titov, 2010), and at least two studies indicate that they are as effective as therapist-led cognitive-behavioral therapy for panic disorder (Craske et al., 2005; Kirotopoulos et al., 2008). However, attrition rates may be higher with self-directed computer/Internet programs in the absence of any therapist contact (e.g., Carlin et al., 2003).

The third setting, the outpatient facility, is most appropriate when conducting very intensive cognitive-behavioral therapy (e.g., daily therapist contact) or treating severely disabled persons who can no longer function at home. In addition, certain medical or drug complications may warrant inpatient treatment. The greatest drawback to the inpatient setting is poor generalization to the home environment. Transition sessions and follow-up booster sessions in an outpatient clinic-office or in the patient’s own home facilitate generalization.

Format

Cognitive-behavioral therapy for panic disorder and agoraphobia may be conducted in individual or group formats. Several clinical outcome studies have used group treatments (e.g., Bohlin, Spindler, Arendt, Houggaard, & Rosenberg, 2009; Craske, DeCola, Sachs, & Pontillo, 2003; Craske et al., 2007; Evans, Holt, & Oei, 1991; Feigenbaum, 1988; Hoffart, 1995; Telch et al., 1993). The fact that their outcomes are generally consistent with the summary statistics obtained from individually formatted treatment suggests that group treatment is as effective as individual therapy. In direct comparisons, albeit few in number, a slight advantage is shown for individual formats. Specifically, Newton, Leroix, and Chaput (1995) compared 12-14 weekly sessions of individual or group cognitive-behavioral therapy (N = 20), although the group condition received two additional 1-hour individual sessions. The two conditions were equally effective for measures of panic and agoraphobia at posttreatment and 6-month follow-up. However, the individual format was more successful in terms of generalized anxiety and depressive symptoms by the follow-up point. In addition, individual treatments resulted in more clinically significant outcomes than group formats in primary care (Sharp, Power, & Swanson, 2004). Furthermore, 95% of individuals assigned to the waiting-list condition in the latter study stated a clear preference for individual treatment when given the choice at the end of the waiting list.

Most studies of cognitive-behavioral therapy for panic and agoraphobia involve 10-20 weekly treatment sessions. Several studies show that briefer treatments may be effective as well. Evans and colleagues (1991) compared a 2-day group cognitive-behavioral treatment to a waiting-list condition, although without random assignment. The 2-day program comprised lectures (3 hours); teaching skills, such as breathing, relaxation, and cognitive challenge (3 hours); in vivo exposure (9 hours); and group discussion plus a 2-hour support group for significant others. Eighty-five percent of treated patients were reported to be either symptom-free or symptomatically improved, and these results were maintained 1 year later. In contrast, the waiting-list group did not demonstrate significant changes. A pilot study similarly indicated effectiveness with intensive cognitive-behavioral therapy over 2 days (Deacon & Abramowitz, 2006). Other studies have evaluated the effectiveness of cognitive-behavioral therapy when delivered over fewer sessions. In a randomized study, patients with panic disorder with agoraphobia who awaited pharmacotherapy treatment were assigned to four weekly sessions of either cognitive-behavioral therapy or supportive nondirective therapy (Craske, Maidenberg, & Bystritsky, 1995). Cognitive-behavioral therapy was more effective than supportive therapy, particularly with less severely affected patients, although the results were not as positive as those typically seen with more sessions. Also, we found that up to six sessions (average of three sessions) of cognitive-behavioral therapy combined with medication recommendations yielded significantly greater improvements on a battery of measures, including quality of life, compared to treatment as usual for individuals with panic disorder in primary care settings (Roy-Byrne, Craske, et al., 2005). Notably, however, the treatment effects substantially increased as the number of cognitive-behavioral therapy sessions (up to six) and follow-up booster and phone call sessions (up to six) increased (Craske et al., 2006). In our subsequent primary care study, an average of seven sessions of cognitive-behavioral therapy and/or medication recommendations was superior to usual care, and in this case, usual care often involved several active treatment elements (Craske et al., 2011). Finally, in a direct comparison, results were equally effective whether cognitive-behavioral therapy was delivered across the standard 12 sessions or across approximately six sessions (Clark et al., 1999).
Interpersonal Context

Interpersonal context variables have been researched in terms of the development, maintenance, and treatment of agoraphobia. The reason for this research interest is apparent from the following vignettes:

“My husband really doesn’t understand. He thinks it’s all in my head. He gets angry at me for not being able to cope. He says I’m weak and irresponsible. He resents having to drive me around, and doing things for the kids that I used to do. We argue a lot because he comes home tired and frustrated from work only to be frustrated more by the problems I’m having. But I can’t do anything without him. I’m so afraid that I’ll collapse into a helpless wreck without him, or that I’ll be alone for the rest of my life. As cruel as he can be, I feel safe around him because he always has everything under control. He always knows what to do.”

This vignette illustrates dependency on the significant other for a sense of safety despite a nonsympathetic response that may only serve to increase background stress for the patient. The second vignette illustrates inadvertent reinforcement of fear and avoidance through attention from the significant other:

“My boyfriend really tries hard to help me. He’s always cautious of my feelings and doesn’t push me to do things that I can’t do. He phones me from work to check on me. He stays with me and holds my hand when I feel really scared. He never hesitates to leave work to help me if I’m having a bad time. Only last week we visited some of his friends, and we had to leave. I feel guilty because we don’t do the things we used to enjoy doing together. We don’t go to the movies anymore. We used to love going to ball games, but now it’s too much for me. I am so thankful for him. I don’t know what I would do without him.”

Perhaps some forms of agoraphobia represent a conflict between desire for autonomy and dependency in interpersonal relationships (Fry, 1962; Goldstein & Chamberless, 1978). In other words, the “pregoraphobic” is trapped in a domineering relationship without the skills needed to activate change. However, the concept of a distinct marital system that predisposes toward agoraphobia lacks empirical evidence. That is not to say that marital or interpersonal systems are unimportant to agoraphobia. For example, interpersonal discord/dissatisfaction may represent one of several possible stressors that precipitate panic attacks. Also, interpersonal relations may be negatively impacted by the development of agoraphobia (Bagliss, Clarke, Henderson, & Presley, 1977) and in turn contribute to its maintenance. Not unlike one of the earlier vignettes, consider the woman who has developed agoraphobia and now relies on her husband to do the shopping and other errands. These new demands upon the husband lead to resentment and marital discord. The marital distress adds to background stress, making progress and recovery even more difficult for the patient.

Aside from whether interpersonal dysregulation contributes to the onset or maintenance of panic disorder or agoraphobia, some studies suggest that poor marital relations adversely impact exposure-based treatments (Bland & Hallam, 1981; Dewey & Hunsley, 1989; Milton & Hafner, 1979). However, other studies show no relationship between marital distress and outcome from cognitive-behavioral therapy (Arrindell & Emmelkamp, 1987; Emmelkamp, 1980; Himadi, Cerny, Barlow, Cohen, & O’Brien, 1986). Another line of research suggests that involving significant others in every aspect of treatment may override potential negative impacts of poor marital relations on phobic improvement (Barlow et al., 1984; Cerny, Barlow, Craske, & Himadi, 1987). Furthermore, involvement of significant others resulted in better long-term outcomes from cognitive-behavioral therapy for agoraphobia (Cerny et al., 1987). Similarly, communications training with significant others, compared to relaxation training, after 4 weeks of in vivo exposure therapy, resulted in significantly greater reductions on measures of agoraphobia by posttreatment (Arnow, Taylor, Agras, & Telch, 1985), an effect that was maintained over an 8-month follow-up. Together, these studies suggest the value of including significant others in the treatment for agoraphobia. On the other hand, treatment focused specifically on interpersonal relationships, via interpersonal therapy, was not as effective as cognitive-behavioral therapy for panic disorder and agoraphobia (Vos, Hubers, Diels, & Arranz, 2012).

Yet another question is the degree to which treatment for panic disorder and agoraphobia influences marital/interpersonal relations. Some have noted that successful treatment can have deleterious effects (Hafner, 1984; Hand & Lamontagne, 1976). Others note that it has no effect or a positive effect on marital functioning (Barlow, O’Brien, & Last, 1984; Himadi et al., 1986).

Therapy:

Only a few in relati onship disorders with agoraphobia involved, i.e., better outcome, an indicator rating on patient Hoogduin. The couple and their relationship is positive or understandable and patient confidence comes, although junior the treatment seems Keijser statements in later session are active and In Session and confines directive s dictated to the patient related to listening to i-come. The patient is the experience: Some believe to therapy is a rectevidence...
and interpersonal functioning in general (Hoffart, 1997). We (Barlow et al., 1983) suggested that when negative effects do occur, it may be because exposure therapy is conducted intensively, without the significant other's involvement, which causes major role changes that the significant other perceives as being beyond his or her control. This again speaks to the value of involving significant others in the treatment process.

**Therapist Variables**

Only a few studies have evaluated therapist variables in relation to cognitive-behavioral treatments for anxiety disorders, let alone panic disorder or agoraphobia. Williams and Chambless (1990) found that patients with agoraphobia who rated their therapists as caring/involved, and as modeling self-confidence, achieved better outcomes on behavioral approach tests. However, an important confound in this study was that patient ratings of therapist qualities may have depended on patient responses to treatment. Keijers, Schaar, Hoogduin, and Lammers (1995) reviewed findings on therapist relationship factors and behavioral outcome. They concluded that empathy, warmth, positive regard, and genuineness assessed early in treatment predicted positive outcome; patients who view their therapists as understanding and respectful improve the most; and patient perceptions of therapist expertise, self-confidence, and directiveness relate positively to outcome, although not consistently. In their own study of junior therapists who provided cognitive-behavioral treatment for panic disorder with or without agoraphobia, Keijers and colleagues found that more empathic statements and questioning occurred in Session 1 than in later sessions. In Session 3, therapists became more active and offered more instructions and explanations. In Session 10, therapists employed more interpretations and confrontations than previously. Most importantly, directive statements and explanations in Session 1 predicted poorer outcome. Empathic listening in Session 1 related to better behavioral outcome, whereas empathic listening in Session 3 related to poorer behavioral outcome. Thus, they demonstrated the advantages of different interactional styles at different points in therapy.

Most clinicians assume that therapist training and experience improve the chances of successful outcome. Some believe this to be the case particularly with respect to the cognitive aspects of cognitive-behavioral therapy (e.g., Michelson et al., 1990), and some indirect evidence for this supposition exists. Specifically, cognitive-behavioral therapy conducted by "novice" therapists in a medical setting (Welkowitz et al., 1991) was somewhat less effective in comparison to the same therapy conducted by inexperienced but highly trained therapists in a psychological setting (Barlow, Craske, Czerny, & Klosko, 1989), or by experienced and highly trained therapists in a community mental health setting (Wade, Treat, & Stuart, 1998). Huppert and colleagues (2001), who directly evaluated the role of therapist experience, found that, in general, therapist experience positively related to outcome, seemingly because these therapists were more flexible in administering the treatment and better able to adapt it to the individual being treated. Obviously, there is a need for more evaluation of the role of therapist experience and training in cognitive-behavioral therapy.

In our primary care work, we developed a computer program to assist novice clinicians in implementing a cognitive-behavioral program for panic disorder (plus other anxiety disorders and depression) (Craske et al., 2009), called Calm Tools for Living. The clinician and patient sit side by side as both view the program on-screen. Throughout, the program prompts clinicians to engage in specific tasks, such as helping patients to establish a fear hierarchy, demonstrating breathing skills, practicing cognitive skills, conducting interoceptive exposure, or designing in vivo exposure assignments. The program also provides learning tools for patients, such as didactic information, interactive exercises, video vignettes, and quizzes. The goal of the computerized program is to enhance the integrity of cognitive-behavioral therapy in the hands of novice and relatively untrained clinicians.

**Patient Variables**

There has been interest in the effect of comorbidity upon the outcomes of cognitive-behavioral therapy for panic disorder and agoraphobia. Brown, Antony, and Barlow (1995) found that comorbidity with other anxiety disorders did not predict response to cognitive-behavioral therapy overall, although social phobia was unexpectedly associated with superior outcome for panic disorder and agoraphobia. In contrast, Tsao, Lewin, and Craske (1998) found a trend for comorbidity that comprised mostly other anxiety disorders to be associated with slightly lower rates of overall success. In a subsequent study, however, we reported the finding by Brown and colleagues of no relationship between baseline comorbidity comprising mostly other anxiety...
disorders, and either immediate or 6-month outcome for panic disorder and agoraphobia (Tsao, Mystkowski, Zucker, & Craske, 2002).

Research on how comorbid depression affects the course and outcome of panic disorder treatment has yielded mixed results. Studies focused on cognitive-behavioral therapy for all anxiety disorders and treatment participation have found that comorbidity with depression is associated with increased rates of refusal to enter treatment (Issakidis & Andrews, 2004); however, once patients have entered treatment, the comorbidity has no effect on rates of attrition (Allen et al., 2010; Brown et al., 1995). Preliminary research investigating the effects of comorbidity on engagement with treatment has revealed that comorbid depression has no effect on compliance with cognitive-behavioral therapy homework (McLean, Woody, Taylor, & Koch, 1998) or compliance with cognitive-behavioral treatment as a whole (Murphy, Michelson, Marchione, Marchione, & Tista, 1998), though it does increase levels of distress associated with treatment (Murphy et al., 1998). Interestingly, comorbid depression has no effect on the response to cognitive-behavioral therapy for panic disorder at posttreatment or follow-up and in both referred and primary care settings (Allen et al., 2010; McLean et al., 1998; Roy-Byrne, Craske, et al., 2005). It seems contradictory that comorbid depression would have significant impact on the severity and persistence of panic disorder (Baldwin, 1998) but would not affect the outcomes of panic disorder treatment. This may be a product of limitations to the current treatment literature. For example, studies have recruited patients for the treatment of panic disorder and have often excluded patients who are very severely depressed or suicidal. Thus, the majority of patients are mildly to moderately depressed. Many of these studies also exclude patients with bipolar disorder, and therefore exclude an entire group of individuals who experience major depressive episodes. However, it may also be that the effects of cognitive-behavioral therapy for panic disorder are sufficiently potent to impact depressive symptoms either directly or indirectly.

A relatively high co-occurrence exists between panic disorder and agoraphobia, and avoidant, dependent, and histrionic personality disorders (e.g., Reich et al., 1994). Questions of diagnostic reliability and validity aside, comorbid personality disorders are sometimes associated with poorer response than usual to cognitive-behavioral therapy for panic disorder or agoraphobia (e.g., Hoffart & Hedley, 1997; Marchand, Goyer, Dupuis, & Main.
guy, 1998). However, closer examination reveals that although individuals with comorbid personality disorders have greater severity of panic or agoraphobia pre- and post-cognitive-behavioral therapy, the rate of decrease in panic or agoraphobia symptoms usually is not affected by the comorbid personality disorder. Thus, Dresen, Arritz, Luttsel, and Salberts (1994) and van den Hout, Bourns, and Oomen (2006) found that comorbid personality disorders did not affect response to cognitive-behavioral therapy for panic or agoraphobia. Moreover, Hofmann and colleagues (1988) found that scores on questionnaire subscales reflecting Axis II personality disorders did not predict panic disorder treatment response to either cognitive-behavioral therapy or to medication. In fact, some personality traits may associate positively with outcome, as was reported by Raths, Sanderson, Miller, and Wetzler (1995) with respect to compulsive personality features.

Substance-related disorders also commonly co-occur with panic disorder and agoraphobia, but very few treatment studies have addressed this important comorbidity. In a series of single cases (N = 3), Lehman, Brown, and Barlow (1998) demonstrated successful control of panic attacks in individuals who were abusing alcohol. Also, the addition of anxiety treatment to a relapse prevention program for abstinent individuals with a primary diagnosis of alcohol dependence and a comorbid diagnosis of panic disorder or social phobia decreased anxiety symptoms relative to a relapse prevention program alone (Schade et al., 2005). However, adding the anxiety treatment did not affect rates of alcohol relapse in that study.

Another source of comorbidity is medical conditions, such as cardiac arrhythmias or asthma, that may slow improvement rates given the additional complications involved in discriminating between anxiety and disease symptomatology, increases in actual medical risk, and the stress of physical diseases. We found that medically ill patients with panic disorder, although more severely affected than their nonmedically ill counterparts at baseline, responded just as favorably to cognitive-behavioral therapy with psychotropic medication recommendations (Roy-Byrne, Stein, et al., 2005). Also, cognitive-behavioral therapy for panic disorder has been shown to alleviate self-reported physical health symptoms (Schmidt et al., 2003). Similarly, we found that cognitive-behavioral therapy and/or psychotropic medication recommendations for anxiety disorders (including panic disorder) significantly improve physical health functioning (Niles et al., 2013).
Other patient variables include socioeconomic status and general living conditions. We evaluated perceived barriers to receiving mental health treatment in our primary care study of panic disorder (Craske, Gollinelli, et al., 2005). Commonly reported barriers included inability to find out where to go for help (43%), worry about cost (40%), lack of coverage by one's health plan (35%), and inability to get an appointment soon enough (35%). Also, in our multicenter trial, attrition from cognitive-behavioral and/or medication treatment for panic disorder with minimal agoraphobia was predicted by lower education, which in turn was dependent on lower income (Grollo et al., 1998). Similarly, levels of education and motivation were associated with dropout rates in another sample, although the effects were small (Keijers, Kampman, & Hoogduin, 2001). Low education-income may reflect less discretionary time to engage in activities such as weekly treatment. Consider a woman who is the mother of two, a full-time clerk, whose husband is on disability due to a back injury, or the full-time student who works an extra 25 hours a week to pay his way through school. Under these conditions, treatment assignments of daily in vivo exposure exercises are much less likely to be completed. Frustration with lack of treatment progress is likely to result. Therapeutic success requires either a change in lifestyle that allows the cognitive-behavioral treatment to become a priority or termination of therapy until a later time, when life circumstances are less demanding. In fact, these kinds of life circumstance issues may explain the trend for African Americans to show less treatment benefit, in terms of mobility, anxiety, and panic attacks, than European Americans (Friedman & Paradis, 1991; Williams & Chambless, 1994). Although, in contrast to these two studies, Friedman, Paradis, and Hatch (1994) found equivalent outcomes across the two racial groups, and the results from another study yielded outcomes from a female African American sample that were judged to be comparable to those of European Americans (Carter, Shrocco, Gore, Marin, & Lewis, 2003). The influence of ethnic and cultural differences on treatment outcome and delivery clearly needs more evaluation.

Finally, patients' understanding of the nature of their problem may be important to the success of cognitive-behavioral treatments. Given the somatic nature of panic disorder, many patients seek medical help first. Beyond that, however, differences in the way the problem is conceptualized could lead to the perception that pharmacological or analytical treatment approaches are more credible than cognitive-behavioral treatment approaches. For example, individuals who strongly believe their condition is due to "a neurochemical imbalance" may be more likely to seek medication and to refuse psychological treatments. Similarly, individuals who attribute their condition to "something about my past—it must be unconscious influences" may resist cognitive-behavioral interpretations. Also, Grollo and colleagues (1998) found that patients with panic disorder or agoraphobia who attributed their disorder to specific stressors in their lives were more likely to drop out of cognitive-behavioral or medication treatment, perhaps because they saw the offered treatment as irrelevant.

**Concurrent Pharmacological Treatment**

Many more patients receive medications than cognitive-behavioral therapy for panic disorder and agoraphobia, partly because primary care physicians are usually the first line of treatment. Thus, one-half or more of patients with panic disorder who attend psychology research clinics already are taking anxiolytic medications. The obvious questions, therefore, are the extent to which cognitive-behavioral therapy and medications have a synergistic effect, and how medications impact cognitive-behavioral therapy.

Results from large clinical trials, including our own multisite trial (Barlow, Gorman, Shear, & Woods, 2000), suggest no advantage during or immediately after treatment of combining cognitive-behavioral and pharmacological approaches. Specifically, both individual cognitive-behavioral and drug treatment, and a combination treatment were immediately effective following treatment. Furthermore, following medication discontinuation, the combination of medication and cognitive-behavioral therapy fared worse than cognitive-behavioral therapy alone, suggesting the possibility that state- (or context-) dependent learning in the presence of medication may have attenuated the new learning that occurs during cognitive-behavioral therapy. In contrast, in the primary care setting, we found that the addition of even just one component of cognitive-behavioral therapy to medications for panic disorder resulted in statistically and clinically significant improvements at posttreatment and 12 months later (Craske, Gollinelli, et al., 2005).

More recently, our multisite collaborative team has been investigating long-term strategies in the treatment of panic disorder. We examined sequential combination
strategies to determine whether this approach is more advantageous than simultaneously combining treatments. In the initial phase, 256 patients with panic disorder and all levels of agoraphobia completed 3 months of initial treatment with cognitive-behavioral therapy (Aaronson et al., 2008; White et al., 2010). Patients were then triaged into two clinical trials. Responders were randomized to 9 months of monthly booster sessions (N = 79) or no booster sessions (N = 78), then followed for an additional 12 months without treatment (White et al., 2013). Booster sessions produced significantly lower relapse rates (52%) and reduced work and social impairment compared to the assessment-only condition without booster sessions (184%) at 21-month follow-up. Multivariate Cox proportional hazards models showed that residual symptoms of agoraphobia at the end of acute-phase treatment were independently predictive of time to relapse during 21-month follow-up (hazard rate = 1.15, p < .01). Thus, booster sessions aimed at reinforcing acute treatment gains to prevent relapse and offset disorder recurrence improved long-term outcome for panic disorder with and without agoraphobia. Fifty-eight of the original patients did not reach an optimal level of functioning (high end-state functioning) and entered a trial in which they received either continued cognitive-behavioral therapy for 3 months or paroxetine for 3 months. Patients doing well with one treatment or the other continued with the respective treatment for an additional 9 months (Payne et al., 2012). Results indicated significantly lower panic disorder symptoms for individuals in the paroxetine condition compared to those in continued cognitive-behavioral therapy at 3 months. However, group differences had disappeared 9 months later. Results were maintained when excluding individuals with comorbid major depression. These data suggest a more rapid treatment response when switching to paroxetine after not responding optimally to cognitive-behavioral therapy; however, both treatments ultimately achieved similar outcomes.

In another study with similar results, patients who did not respond to cognitive-behavioral therapy also benefited more from the addition of a serotonergic drug (paroxetine) to continued cognitive-behavioral therapy than from the addition of a drug placebo, with substantially different effect sizes (Kampman, Keijzer, Hoogduin, & Hendriks, 2002). Conversely, individuals who are resistant to pharmacotherapy may respond positively to cognitive-behavioral therapy, although these findings were part of an open trial without randomization (Heldt et al., 2006).

Findings from the combination of fast-acting anxiolytics, specifically, the high-potency benzodiazepines, and behavioral treatments for agoraphobia are contradictory (e.g., Marks et al., 1993; Wardle et al., 1994). Nevertheless, several studies have reliably demonstrated the detrimental effects of chronic use of high-potency benzodiazepines on short-term and long-term outcome in cognitive-behavioral treatments for panic or agoraphobia (e.g., Otto, Pollack, & Sabatino, 1996; van Balkom, de Beurs, Koole, Lange, & van Dyck, 1996; Wardle et al., 1994). Specifically, there is evidence for more attrition, poorer outcome, and more relapse with chronic use of high-potency benzodiazepines. In addition, use of benzodiazepines as needed was associated with poorer outcome than regular use or no use in one small naturalistic study (Westra, Stewart, & Conrad, 2002).

Finally, the cost-effectiveness of cognitive-behavioral and medication treatments alone rather than in combination requires further evaluation; currently, cognitive-behavioral therapy is considered to be more cost-effective (e.g., disability costs, work days missed, health care use) than pharmacotherapy (Heenroozer et al., 2004).

Understanding the ways in which psychotropic medications influence cognitive-behavioral therapy may prove useful for developing methods that optimize the combination of these two approaches to treatment. First, medications, particularly fast-acting, potent medications that cause a noticeable shift in state and are used on an as-needed basis (e.g., benzodiazepines, beta-blockers), may contribute to relapse because therapeutic success is attributed to them rather than to cognitive-behavioral therapy. Patients’ resultant lack of perceived self-control may increase relapse potential when medication is withdrawn or contribute to maintenance of a medication regimen under the assumption that it is necessary to functioning. In support, attribution of therapeutic gains to alprazolam, and lack of confidence in coping without alprazolam, even when given in conjunction with behavioral therapy, predicted relapse (Baloglu, Marks, Kilic, Brewin, & Swinson, 1994). Second, medications may assume the role of safety signals, or objects to which persons erroneously attribute their safety from painful, aversive outcomes. Safety signals may contribute to maintenance of fear and avoidance in the long term (Hermans, Craske, Mineka, & Lovibond, 2006) and may interfere with corrections of misappraisals of bodily symptoms (see below for further discussion of this issue). Third,
medications may reduce the motivation to engage in practices of cognitive-behavioral skills, yet completion of between-session assignments is a positive predictor of outcome from cognitive-behavioral therapy (e.g., Glenn et al., in press). Finally, learning that takes place under the influence of medications may not necessarily generalize to the time when medications are removed, thus contributing to relapse (Bouton & Swartz, 1994). Some of these points are illustrated in the following vignettes:

“Had been through a program of cognitive-behavioral therapy, but it was really the Paxil that helped. Because I was feeling so much better, I considered tapering off the medication. At first I was very concerned about the idea. I had heard horror stories about what people go through when withdrawing. However, I thought it would be OK as long as I tapered slowly. So, I gradually weaned myself off. It really wasn’t that bad. Well, I had been completely off the medication for about a month when the problem started all over again. I remember sitting in a restaurant, feeling really good because I was thinking about how much of a problem restaurants used to be for me before, and how easy it seemed now. Then, wham! I became very dizzy and I immediately thought, ‘Oh no, here it comes.’ I had a really bad panic attack. All I could think of was why didn’t I stay on the medication?”

“I started to lower my dose of Xanax. I was OK for the first couple of days... I felt really good. Then, when I woke up on Friday morning, I felt strange. My head felt really tight and I worried about having the same old feelings all over again. The last thing I want to do is to go through that again. So I took my usual dose of Xanax and, within a few minutes, I felt pretty good again. I need the medication. I can’t manage without it right now.”

In what ways might such negative effects of medications be offset? One possibility is that continuation of exposure after medication is withdrawn may offset relapse because it enhances attributions of personal mastery and reduces the safety signal function of medications. In addition, opportunities to practice exposure and cognitive and behavioral strategies without the aid of medication overcome state dependency and enhance generalization of therapeutic gains once treatment is over.

**CASE STUDY**

Julie, a 33-year-old European American mother of two, lives with Larry, her husband of 8 years. For the past 3 years she has been chronically anxious and panic stricken. She describes her panic attacks as unbearable and increasing in frequency. The first time she felt panicky was just over 3 years ago, when she was rushing to be by her grandmother’s side in the last moments before she died. Julie was driving alone on the freeway. She remembers feeling as if everything were moving in slow motion, as if the cars were standing still, and things around her seemed unreal. She recalled feeling short of breath and detached. However, it was so important to reach her destination that she did not dwell on how she felt until later. After the day was over, she reflected on how lucky she was not to have had an accident. A few weeks later, she experienced the same feeling again when driving on the freeway. This time it occurred without the pressure of getting to her dying grandmother. It scared Julie because she was unable to explain the feelings. She pulled to the side of the road and called her husband, who came to meet her. She followed him home, feeling anxious the entire way.

Now, Julie has these feelings in many situations. She describes her panic attacks as feelings of unreality, detachment, shortness of breath, a racing heart, and a general fear of the unknown. It is the unreality that scares her the most. Consequently, Julie is sensitive to anything that produces “unreal” types of feelings, such as the semi-consciousness that occurs just before falling asleep, the period when daylight changes to night, bright lights, concentrating on the same thing for long periods of time, alcohol or drugs, and being anxious in general. Even though she has a prescription for Klonopin (a high-potency benzodiazepine), she rarely, if ever, uses it because of her general fear of being under the influence of a drug or of feeling an altered state of consciousness. 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 way of managing her panic. She does not leave home without the Klonopin. Julie 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 stimulating and racy effects. She was never a big exerciser, but to think of exerting herself now is also scary. Julie reports that she is constantly waiting for the next panic attack to occur. She avoids freeways, driving on familiar surface...
streets only. She limits herself to a 10-mile radius 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 to panic in front of others. In general, she prefers to be with her husband or her mother. However, she can do most things as long as she is within her "safety" region.

Julie describes how she differs from the way she used to be: how weak and scared she is now. The only other incident that is similar to her current panic attacks occurred in her early 20s, when she had a negative reaction to smoking marijuana. Julie became very scared of the feeling of losing control and feared that she would never return to reality. She has not taken drugs since then. Otherwise, there is no history of serious medical conditions or any previous psychological treatment. Julie had some separation anxiety and was shy as a young child and throughout her teens. However, her social anxiety improved throughout her 20s to the point that until the onset of her panic attacks, she was mostly very comfortable around people. Since the onset of her panic attacks, Julie has become concerned that others will notice that she appears anxious. However, her social anxiety is limited to panic attacks and does not reflect a broader social phobia.

In general, Julie's appetite is good, but her sleep is restless. Once again, a week or more ago she woke up abruptly in the middle of the night, feeling short of breath and scared, and she has great difficulty going to sleep when her husband travels. In addition to worrying about her panic attacks, Julie worries about her husband and her children, although these latter worries are secondary to her worry about panic and not excessive. She has some difficulty concentrating but is generally able to function at home and at work because of the familiarity of her environment and the safety she feels in the presence of her husband. Julie works part time as the manager of a business that she and her husband own. She sometimes becomes depressed about her panic and the limitations on how far she can travel. Occasionally, she feels hopeless about the future, doubting whether she will ever be able to escape the anxiety. Although the feelings of hopelessness and the fearfulness never last more than a few days, Julie has generally had a low-grade depressed mood since her life became restricted by the panic attacks.

Julie's mother and her uncle both had panic attacks when they were younger. Julie is now worried that her oldest child is showing signs of being overly anxious because he is hesitant about trying new things or spending time away from home.

**Assessment**

A functional behavioral analysis depends on several different modes of assessment, which we describe next.

**Interviews**

An in-depth interview is the first step in establishing diagnostic features and the profile of symptomatic and behavioral responses. Several semistructured and fully structured interviews exist. The Anxiety Disorders Interview Schedule for DSM-IV (ADI-S; Di Nardo, Brown, & Barlow, 1994) and for DSM-5 (ADIS-5; Brown & Barlow, in press) primarily assesses anxiety disorders, as well as mood and somatoform disorders. Psychotic and drug conditions are screened by this instrument as well. The ADIS facilitates gathering the necessary information to make a differential diagnosis among anxiety disorders and offers a means to distinguish between clinical and subclinical presentations of a disorder. Data on the frequency, intensity, and duration of panic attacks, as well as details on avoidance behavior, are embedded within the ADIS; this information is necessary for tailoring treatment to each individual's presentation. The value of structured interviews is their contribution to a differential diagnosis and interrater reliability. Interrater agreement ranges from satisfactory to excellent for the various anxiety disorders using the ADIS (Brown, Di Nardo, Lehman, & Campbell, 2001). Similar analysis for the ADIS-5 are under way.

Similarly, the Schizophrenia and Affective Disorders Schedule—Lifetime Version (modified for the study of anxiety) produces reliable diagnoses for most of the anxiety disorders (generalized anxiety disorder and simple phobia are the exceptions) (Manuzza, Fyer, Liebowitz, & Klein, 1990), as does the Structured Clinical Interview for DSM (SCID), which covers all of the mental disorders (First, Spitzer, Gibbon, & Williams, 1994), and will be updated for DSM-5 diagnostic criteria.

Differential diagnosis is sometimes difficult because, as described earlier, panic is a ubiquitous phenomenon (Barlow, 1988) that occurs across a wide variety of emotional disorders. It is not uncommon for persons with specific phobias, social phobia, generalized anxiety disorder, obsessive-compulsive disorder, and posttraumatic stress disorder to report panic attacks. For Julie, there was a differential diagnostic question regarding social anxiety disorder, and panic disorder and agoraphobia. Shown in Figure 1.1 are the ADIS-IV questions that address this differentiation (Julie's answers are in italics).
Parts of ADIS-IV Panic Disorder Section

Do you currently have times when you feel a sudden rush of intense fear or discomfort? Yes.

In what kinds of situations do you have those feelings? Driving, especially on freeways... alone at home... at parties or in crowds of people.

Did you ever have those feelings come "from out of the blue," for no apparent reason, or in situations where you did not expect them to occur? Yes.

How long does it usually take for the rush of fear/discomfort to reach its peak level? It varies, sometimes a couple of seconds and at other times it seems to build more slowly.

How long does the fear/discomfort usually last at its peak level? Depends on where I am at the time. If it happens when I'm alone, sometimes it's over within a few minutes or even seconds. If I'm in a crowd, then it seems to last until I leave.

In the last month, how much have you been worried about, or how fearful have you been about having another panic attack?

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No worry</td>
</tr>
<tr>
<td>1</td>
<td>Rarely worried/mild fear</td>
</tr>
<tr>
<td>2</td>
<td>Occasionally worried/moderate fear</td>
</tr>
<tr>
<td>3</td>
<td>Frequently worried/severe fear</td>
</tr>
<tr>
<td>4</td>
<td>Constantly worried/extreme fear</td>
</tr>
</tbody>
</table>

Parts of ADIS-IV Social Phobia Section

In social situations, where you might be observed or evaluated by others, or when meeting new people, do you feel fearful, anxious, or nervous? Yes.

Are you overly concerned that you might do and/or say something that might embarrass or humiliate yourself in front of others, or that others may think badly of you? Yes.

What are you concerned will happen in these situations? That others will notice that I am anxious. My face turns white and my eyes look strange when I panic. I am worried that I'll pass out in front of them, and they won't know what to do.

Are you anxious about these situations because you are afraid that you will have an unexpected panic attack? Yes (either a panic or that I'll feel unreal).

Other than when you are exposed to these situations, have you experienced an unexpected rush of fear/anxiety? Yes.

FIGURE 1.1. Julie’s responses to ADIS-IV questions.

As demonstrated in Figure 1.1, Julie experiences panic attacks in social situations and is concerned about being negatively evaluated by others if her anxiety becomes visibly apparent. However, despite her history of shyness, Julie’s current social discomfort is based primarily on the possibility of panicking. Because of this, and because she meets the other criteria for panic disorder (i.e., unexpected nonsocial panic attacks and pervasive apprehension about future panic attacks), the social distress is best subsumed under the domain of panic disorder and agoraphobia. If Julie reported that she experiences panic attacks in social situations only, or that she worries about panic attacks in social situations only, then a diagnosis of social anxiety disorder...
would be more probable. A report of unexpected panic attacks, as well as self-consciousness about things that she might do or say in social situations regardless of the occurrence of panic, would be consistent with a dual diagnosis of panic disorder—agoraphobia and social anxiety disorder. In general, an individual with panic disorder may continue to feel anxious even when playing a passive role in a social setting, whereas a patient with social phobia is more likely to feel relaxed when he or she is not the center of attention and does not anticipate being evaluated or judged (Dattilio & Salas-Auvert, 2000).

The same types of diagnostic questioning are useful for distinguishing between panic disorder—agoraphobia and claustrophobia. Other differential diagnostic issues can arise with respect to somatoform disorders, real medical conditions, and avoidant or dependent personality disorders.

Following completion of a diagnostic assessment, a dimensional assessment specifically designed for panic disorder, such as the Panic Disorder Severity Scale (PDSS; Shear et al., 1997), may be helpful. This clinician-completed scale rates seven areas of responding using a 0- to 4-point severity rating scale: panic attack frequency; distress; anticipatory anxiety; agoraphobic and interoceptive-related fears; avoidant behavior; and work and social impairment. A cutoff score of 8 on the PDSS identifies patients with panic disorder with high sensitivity and acceptable specificity (Shear et al., 2001).

Medical Evaluation

A medical evaluation is generally recommended because several medical conditions should be ruled out before assigning the diagnosis of panic disorder. 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, although panic disorder is likely to continue even when the symptoms are under medical control. Mitral valve prolapse, asthma, allergies, and hypoglycemia fall into this latter category. According to the model described earlier, these medical conditions exacerbate panic disorder to the extent that they elicit the feared physical sensations. For example, mitral valve prolapse sometimes produces the sensation of a heart flutter, asthma produces shortness of breath, and hypoglycemia produces dizziness and weakness, all of which overlap with symptoms of panic and may therefore become conditional cues for panic.

Self-Monitoring

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. In contrast, ongoing self-monitoring generally yields more accurate, less inflated estimates (for a comprehensive review of self-monitoring for panic and anxiety, see Craske & Tsao, 1999). Also, ongoing self-monitoring is believed to contribute to an objective self-awareness. Objective self-monitoring replaces negative, affect-laden self-statements such as “I feel horrible. This is the worst it has ever been—my whole body is out of control!” with “My anxiety level is 6. My symptoms include tremulousness, dizziness, unreal feelings, and shortness of breath—and this episode lasted 10 minutes.” Objective self-awareness usually reduces negative affect. Finally, self-monitoring provides feedback for judging progress and useful material for in-session discussions.

Panic attacks are recorded in the Panic Attack Record, a version of which is shown in Figure 1.2. This record, which is to be completed as soon as possible after a panic attack occurs, is therefore carried on person (wallet size). Daily levels of anxiety, depression, and worry about panic are monitored with the Daily Mood Record shown in Figure 1.3. This record is completed at the end of each day. Finally, activities may be recorded by logging daily excursions in a diary, or by checking off activities completed from an agoraphobia checklist.

A common problem with self-monitoring is noncompliance. Sometimes noncompliance is due to misunderstanding or lack of perceived credibility in self-monitoring. Most often, however, noncompliance is due to anticipation of more anxiety as a result of monitoring. This is particularly true for individuals whose preferred style of coping is to distract themselves as much as possible because thought of panic might otherwise become overwhelming: “Why should I make myself worse by asking myself how bad I feel?” In Julie’s case, the self-monitoring task was particularly difficult because explicit reminders of her anxiety elicited strong
Panic Disorder and Agoraphobia

Date 2/16/06  Time began 5:20 PM
Triggers Home alone and shortness of breath
Expected x Unexpected

Maximum Fear 0—1—2—3—4—5—6—7—8—9—10
None  Mild  Moderate  Strong  Extreme

Check all symptoms present to at least a mild degree:
Chest pain or discomfort x
Heart racing/palpitations/pounding x
Short of breath x
Shaking/trembling x
Numbness/tingling
Feelings of choking
Fear of losing control/going crazy x

Thoughts: I am going crazy, I will lose control
Behaviors: Called my mother

FIGURE 1.2. Julie's Panic Attack Record.

<table>
<thead>
<tr>
<th>Date</th>
<th>Average anxiety</th>
<th>Average depression</th>
<th>Average worry about panic</th>
</tr>
</thead>
<tbody>
<tr>
<td>2/16</td>
<td>7</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>2/17</td>
<td>5</td>
<td>4</td>
<td>5</td>
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<td>2/18</td>
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<td>4</td>
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<td>2/19</td>
<td>4</td>
<td>3</td>
<td>4</td>
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<td>4</td>
<td>4</td>
<td>5</td>
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<tr>
<td>2/21</td>
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<td>1</td>
</tr>
<tr>
<td>2/22</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

FIGURE 1.3. Julie's Daily Mood Record.
concerns about losing touch with reality. Prompting reassurance that anxiety would subside with perseverance at self-monitoring and emphasis on objective versus subjective self-monitoring were helpful for Julie. In addition, therapist attention to the self-monitored information and corrective feedback about the method of self-monitoring at the start of each treatment session reinforced Julie's self-monitoring.

**Standardized Inventories**

Several standardized self-report inventories provide useful information for treatment planning and are sensitive markers of therapeutic change. The Anxiety Sensitivity Index (Reiss, Peterson, Gurisky, & McNally, 1986) and the multidimensional Anxiety Sensitivity Index-3 (Taylor et al., 2007) have received wide acceptance as a trait measure of threatening beliefs about bodily sensations. Both display sound psychometric properties and tend to discriminate panic disorder and agoraphobia from other anxiety disorders (e.g., Taylor et al., 1992; Telch, Sherman, & Lucas, 1989), especially the Physical Concerns subscale (Zinbarg et al., 1997). More specific information about which particular bodily sensations are feared most and what specific misappraisals occur most often may be obtained from the Body Sensations Questionnaire and the Agoraphobia Cognitions Questionnaire, respectively (Chambless, Caputo, Bright, & Gallagher, 1984). Both scales have strong to excellent psychometric properties and are sensitive to change following treatment (see Keller & Craske, 2008). The Mobility Inventory (Chambless, Caputo, Gracely, Jasin, & Williams, 1985) lists agoraphobic situations, which are rated in terms of degree of avoidance when alone and when accompanied. This instrument is very useful for establishing in vivo exposure hierarchies and, again, is well supported psychometrically.

In addition, we have developed two standardized self-report inventories that are useful for panic disorder and agoraphobia. The first, the Albany Panic and Phobia Questionnaire (Rapee, Craske, & Barlow, 1995), assesses fear and avoidance of activities that produce feared bodily sensations (e.g., exercise, caffeine), as well as more typical agoraphobic and social situations. Factor analyses confirmed three distinct factors labeled Agoraphobia, Social Phobia, and Interoceptive Fears. The questionnaire has adequate psychometric properties and is useful in profiling agoraphobic versus interoceptive avoidance. The second, the Anxiety Control Questionnaire, assesses perceived lack of control over anxiety-related events and occurrences, such as internal emotional reactions or externally threatening cues (Rapee, Craske, Brown, & Barlow, 1996). This scale is designed to assess locus of control, but in a more specific and targeted manner relevant to anxiety and anxiety disorders compared to more general locus-of-control scales. A revised 15-item version yields three factors—Emotion Control, Threat Control, and Stress Control—with a higher-order dimension of perceived control (Brown, White, Forsyth, & Barlow, 2004). Changes in this scale from pre to posttreatment predicted reductions in comorbidity at follow-up in one study (Craske et al., 2007). A more detailed review of each questionnaire listed herein and the complete assessment for panic disorder and agoraphobia is provided by Keller and Craske (2008).

**Behavioral Tests**

The behavioral test is a useful measure of degree of avoidance of specific interoceptive cues and external situations. Behavioral approach tests can be standardized or individually tailored. The standardized behavioral test for agoraphobic avoidance usually involves walking or driving a particular route, such as a 1-mile loop around the clinic setting. Standardized behavioral tests for anxiety about physical sensations involve exercises that induce panic-like symptoms, such as spinning in a circle, running in place, hyperventilating, and breathing through a straw (Barlow & Craske, 2006). Anxiety levels are rated at regular intervals throughout the behavioral tests, and actual distance or length of time is measured. The disadvantage of standardized behavioral tests is that the specific task may not be relevant to all patients (e.g., a 1-mile walk or running in place may be only mildly anxiety provoking to some but highly distressing to others); hence, the value of individually tailored tasks. In the case of agoraphobia, this usually entails attempts at three to five individualized situations that the patient has identified as ranging from somewhat difficult to extremely difficult, such as driving two exits on freeway, waiting in a bank line, or shopping in a local supermarket for 15 minutes. For anxiety about physical sensations, individually tailored behavioral tests entail exercises designed specifically to induce the sensations feared most by a given patient (e.g., nose pugs to induce sensations of difficulty breathing). As with standardized tests, ongoing levels of anxiety and degree of approach behavior are mean-
sured in relation to individually tailored behavioral tests.

Individually tailored behavioral tests are more informative for clinical practice, although they confound between-subject comparisons for research purposes. Behavioral tests are an important supplement to self-report of agoraphobic avoidance because patients tend to underestimate what they can actually achieve (Craske et al., 1988). In addition, behavioral tests often reveal important information for treatment planning of which the individual is not yet fully aware. For example, the tendency to remain close to supports, such as railings or walls, may not be apparent until one observes the patient walking through a shopping mall. In Julie’s case, the importance of change from daylight to night was not apparent until she was asked to drive on a section of road as a behavioral test. Her response was that it was too late in the day to drive because dusk made her feel as if things were unreal. Similarly, it was not until Julie completed a behavioral test that we recognized the importance of air-conditioning when she was driving. Julie believed that the cool air blowing on her face helped her to remain “in touch with reality.” Finally, we noticed that her physical posture while driving was a factor that contributed to anxiety: Julie’s shoulders were hunched, and she leaned toward the steering wheel and held it very tightly. All of these were targeted in the treatment: Driving at dusk was included in her hierarchy; air-conditioning was regarded as a safety signal from which she should be weaned; and driving in a more relaxed position was part of mastery exposure.

Functional Analysis

The various methods of assessment provide the material for a full functional analysis for Julie. Specifically, the topography of her panic attack is as follows: The most common symptoms include a feeling of unreality, shortness of breath, and racing heart. Average frequency of panic attacks is three per week; each panic attack on average lasts from a few seconds to 5 minutes, if Julie is not in a crowd, where the panic attacks last until she exits the crowd; in terms of apprehension, Julie worries about panic 75% of the day; and most of her panic attacks are expected, but she has some unexpected ones as well. Julie has both situational and internal antecedents to her panic attacks. The situational antecedents include driving on freeways; crowds of people; being alone, especially at night; restaurants; dusk; reading and concentrating for long periods of time; and aerobic activity. The internal antecedents include heart rate fluctuations, lightheaded feelings, hunger feelings, weakness due to lack of food, thoughts of the “big one” happening, thoughts of not being able to cope with this for much longer, and anger. Her misappraisals about panic attack symptoms include beliefs that she will never return to normality, that she will go crazy or lose control, and that others will think she is weird. Her behavioral reactions to panic attacks include escape behaviors such as pulling off to the side of the road, leaving restaurants and other crowded places, calling her husband or mother, and checking for her Klonopin. Her behavioral reactions to the anticipation of panic attacks include avoidance of driving long distances alone, driving on unfamiliar roads and freeways, at dusk, crowded areas, exercise, quiet time with nothing to do, and doing one thing for a long period of time. In addition, she tries not to think about anxiety or feelings of unreality. Her safety signals and safety-seeking behaviors include having her Klonopin on hand at all times, always knowing the location of her husband, and having the air-conditioning on. The consequences of her panic disorder with agoraphobia affect her family. Julie’s husband is concerned and supportive, but her mother thinks she should pull herself together because “it’s all in her head.” In addition, Julie works but has cut back the number of hours, and she travels and socializes much less. Her general mood includes some difficulty concentrating and sleeping, restlessness, headaches, and muscular pains and aches. In addition, she is occasionally tearful, sad, and hopeless, and generally feels down.

Psychophysiology

Ongoing physiological measures are not very practical tools for clinicians, but they can provide important information. In particular, the discrepancy described earlier between reports of symptoms and actual physiological arousal (i.e., report of heart rate acceleration in absence of actual heart rate acceleration) may serve as a therapeutic demonstration of the role of attention and cognition in symptom production. Similarly, actual recordings provide data to disconfirm misappraisals such as “My heart feels like it’s 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, resting levels of physiological functioning, which are sometimes dysregulated in anxious individuals, may be sensitive measures of treatment outcome (e.g., Craske, Lang, et al., 2005).
COMPONENTS OF COGNITIVE-BEHAVIORAL THERAPY

The components of the cognitive-behavioral treatment described in this section are integrated into a session-by-session treatment program in the next section.

Education

The treatment begins with education about the nature of panic disorder, the causes of panic and anxiety, and the ways panic and anxiety are perpetuated by feedback loops among physical, cognitive, and behavioral response systems. In addition, specific descriptions of the psychophysiology of the fight-flight response are provided, as well as an explanation of the adaptive value of the various physiological changes that occur during panic and anxiety. The purpose of this education is to correct the common myths and misconceptions about panic symptoms (i.e., beliefs about going crazy, dying, or losing control) that contribute to panic and anxiety. The survival value of alarm reactions (i.e., panic attacks) is emphasized throughout.

Education also differentiates between the state of anxiety and the emotion of fear/panic, both conceptually and in terms of its three response modes (subjective, physiological, and behavioral). This distinction is central to the model of panic disorder and to the remainder of the treatment. Anxiety is viewed as a state of preparation for future threat, whereas panic is the fight-flight emotion elicited by imminent threat. Panic/fear is characterized by perceptions of imminent threat, sudden autonomic discharge, and fight-flight behavior. In contrast, anxiety is characterized by perceptions of future threat and chronic tension, caution, avoidance, and disruption of performance.

Self-Monitoring

Self-monitoring is essential to the personal scientist model of cognitive-behavioral therapy. Self-monitoring is introduced as a way to enhance objective self-awareness and increase accuracy in self-observation. As noted earlier, patients are asked to keep at least two types of records. The first, the Panic Attack Record, is completed as soon after each panic attack as possible; this record provides a description of cues, maximal distress, symptoms, thoughts, and behaviors. The second, the Daily Mood Record, is completed at the end of each day to record overall or average levels of anxiety, depression, and whatever else is considered important to record. Additionally, patients may keep a daily record of activities or situations completed or avoided.

Breathing Retraining and Capnometry-Assisted Respiratory Training

Breathing retraining is a central component early on in the development of panic control treatments because many panic patients describe symptoms of hyperventilation as being very similar to their panic attack symptoms. It is noteworthy, however, that a hyperventilation symptom report does not always accurately represent hyperventilation physiology: Only 50% or fewer patients show actual reductions in end-tidal CO₂ values during panic attacks (Hibbert & Plisbey, 1980; Holt & Andrews, 1980; Hornsveld, Garssen, Piekelen, Dop, & van Spiegel, 1980).

In early conceptualizations, panic attacks were related to stress-induced respiratory changes that provoke fear either because they are perceived as threatening or they augment fear already elicited by other phobic stimuli (Clark, Salkovskis, & Chalkley, 1985). Several studies illustrated a positive effect of breathing retraining, involving slow abdominal breathing exercises (e.g., Kraft & Hoogduin, 1984). The value of breathing retraining was subsequently questioned. For example, several studies suggested that the addition of breathing retraining alone did not improve on in vivo exposure (e.g., de Beurs, van Balkom, Lange, Koele, & van Dyck, 1995). Phases breathing retraining to be slightly less effective than interoceptive exposure when each was added to cognitive restructuring and in vivo exposure (Craske, Rowe, Lewis, & Noriega-Dimitri, 1997), and in another study, the inclusion of breathing retraining resulted in poorer outcomes than cognitive-behavioral therapy without breathing retraining, although the findings were not robust (Schmidt et al., 2000). From their review of efficacy and mechanisms of action, Garssen, de Ruiter, and van Dyck (1992) concluded that breathing retraining probably affects change not through breathing per se but through distraction and/or a sense of control. Thus, breathing retraining is no longer considered a central component of cognitive-behavioral therapy for panic disorder. Furthermore, to the extent that it might become misused as a means for avoiding physical symptoms, it may even be countertherapeutic. That being said, there may be occasions when breathing retraining is a useful tool, such as for the individual showing obvious signs of irregular breathing (e.g.,
rapid, shallow breathing, frequent deep breaths), as long as breathing retraining does not become a method of avoidance or safety seeking.

In contrast to traditional breathing retraining, capnometry-assisted respiratory training (CART) targets respiratory dysregulation, in particular hypocapnia (Meuret, Rosenfield, Siedel, Bhaskara, & Hofmann, 2010; Meuret, Wilhelm, Ritz, & Roth, 2008). CART is a brief, 4-week training that uses immediate feedback of end-tidal partial pressure of CO2 (pCO2) to teach patients how to raise their subnormal levels of pCO2 (hyperventilation) and thereby gain control over dysregulated respiratory patterns and associated panic symptoms (e.g., shortness of breath, dizziness). The device, a portable capnometer, offers breath-by-breath feedback of expired CO2 and rate of breathing (both measured via a nasal cannula). Due to the novelty of CART, randomized controlled trials are limited but promising. In a first randomized-controlled study, Meuret and colleagues (2008) tested the efficacy of 4 weeks of CART (N = 20) compared to a delayed waitlist control group (WL, N = 17). CART, but not WL, led to sustained increases in pCO2 levels and reduced panic severity and frequency. Reductions in panic symptom severity (PDSS; Shear et al., 1997) were comparable to standard cognitive-behavioral therapy, and improvements were maintained at 12-month follow-up. In a second study, patients with panic disorder were randomly assigned to receive either 4 weeks of CART (N = 21) or cognitive therapy (N = 20). An initial 4 weeks of skills training was followed by three sessions of in vivo exposure and a fourth session at a 2-months follow-up. Respective skills acquisition trainings led to significant and comparable reductions in panic symptom severity and panic-related cognitions, irrespective of modality. However, only CART, not cognitive therapy, led to a correction of hypocapnic levels of pCO2 (Meuret et al., 2010; Siedel, Rosenfield, Bhaskara, Hofmann, & Meuret, 2009). However, an evaluation of the degree to which CART augments exposure therapy (relative to exposure therapy alone) awaits testing.

Applied Relaxation

A form of relaxation known as applied relaxation has shown good results as a treatment for panic attacks. Two studies by Ost (Ost & Westling, 1995; Ost, Westling, & Hofmann, 1993) indicate that applied relaxation is as effective as in vivo exposure and cognitive therapy. In contrast, Barlow and colleagues (1989) found that applied progressive muscle relaxation (PMR) is relatively ineffective for panic attacks, although we excluded all forms of interoceptive exposure from the hierarchy of tasks to which PMR was applied, which was not necessarily the case in the studies by Ost. Clark and colleagues (1994) found cognitive therapy to be superior to applied PMR when conducted with equal amounts of in vivo exposure, whereas Beck, Stanley, Baldwin, Deagle, and Averill (1994) found very few differences between cognitive therapy and PMR when each was administered without exposure procedures.

Cognitive Restructuring

Cognitive restructuring is a skills set in which patients learn to recognize cognitive errors and generate alternative, noncatastrophic explanations for the sensations that are feared during panic attacks. Cognitive therapy begins with a treatment rationale and discussion of the role of thoughts in generating emotions. Next, thoughts are recognized as hypotheses rather than as fact, and are therefore open to be questioned and challenged. Detailed self-monitoring of emotions and associated cognitions is instituted to identify specific beliefs, appraisals, and assumptions. Once identified, relevant cognitions are categorized into types of typical errors that occur during heightened emotion, such as overestimations of risk of negative events or catastrophization of meaning of events. The process of categorization, or labeling of thoughts, is consistent with a personal scientist model and facilitates an objective perspective by which the validity of the thoughts can be evaluated. Thus, in labeling the type of cognitive distortion, the patient is encouraged to use an empirical approach to examine the validity of his or her thoughts by considering all of the available evidence. Therapists use Socratic questioning to help patients make guided discoveries and question their anxious thoughts. Next, more evidence-based alternative hypotheses are generated. In addition to surface-level appraisals (e.g., “That person is frowning at me because I look foolish”), core-level beliefs or schemas (e.g., “I am not strong enough to withstand further distress” or “I am unlikable”) are questioned in the same way. Importantly, cognitive restructuring is not intended as a direct means of minimizing fear, anxiety, or unpleasant symptoms. Instead, cognitive restructuring is intended to correct distorted thinking; eventually fear and anxiety are expected to subside, but their diminution is not the first goal of cognitive therapy.
Cognitive therapy is often intermingled with behavioral techniques (e.g., "behavioral experiments," "hypothetical testing," "instructions" involving exposure) that complicate direct testing of the efficacy of cognitive therapy in its "pure" form (e.g., Hofhart, Sexton, Hedley, & Martens, 2008; Hofman et al., 2007; Öst et al., 1993; Teachman, Marker, & Smith-Junik, 2008). Nonetheless, there is some evidence that training in cognitive procedures in full isolation from exposure and behavioral procedures is efficacious in reducing aspects of panic (Beck et al., 1994; Meuret et al., 2010; Salkovskis, Clark, & Hackmann, 1991; van den Hout, Arritz, & Hoekstra, 1994). Similarly, in a study by Bouchard and colleagues (1996), cognitive restructuring was as effective as exposure therapy in reducing panic symptoms. However, the effects of cognitive therapy alone on agoraphobia are unclear. One study found that cognitive therapy was less effective than exposure therapy for agoraphobia (Williams & Falbo, 1996). Another study (Hoffart, 1995) found that cognitive therapy was an effective as guided mastery exposure delivered intensively over 6 weeks for individuals with moderate to severe agoraphobia, although some elements of exposure (e.g., hyperventilation tests to elicit sensations) were included in the cognitive therapy condition.

A series of studies have evaluated the effects of cognitive therapy combined with exposure in comparison to exposure alone or in combination with other coping skills. Most often, cognitive therapy combined with exposure does not yield an additional benefit over in vivo exposure alone (Öst, Thulin, & Rammero, 2004; van den Hout et al., 1994; see Murphy et al., 1998, for an exception).

**Exposure**

Exposure is a critical phase of treatment and, once begun, is a major factor of treatment sessions as well as between-treatment session homework, since limited exposure practice is of small benefit and may even be detrimental. The exposure is designed to disconfirm misappraisals and extinguish conditioned emotional responses to external situations and contexts, through in vivo exposure, as well as to bodily sensations, through interoceptive exposure. Growing evidence suggests that exposure represents the most powerful component of cognitive-behavioral therapy for panic disorder and agoraphobia, including meta-analyses that fail to show any additional benefit of either cognitive restructuring or somatic coping skills beyond exposure therapy alone (Norton & Price, 2007). A large trial reported a dose-response relationship between exposure and improvement in agoraphobia (Gloster et al., 2011).

**In Vivo Exposure**

In vivo exposure refers to repeated and systematic, real-life exposure, in this case, to agoraphobic situations. A long history of research has established the efficacy of in vivo exposure for agoraphobia.

Most often, in vivo exposure is conducted in a graduated manner, proceeding from the least to the most anxiety-provoking situations on an avoidance hierarchy. However, there is some evidence to suggest that intensive or ungraded exposure may be effective. In a study by Feigenbaum (1988), treatment sessions were conducted in a massed format over the course of 6-10 consecutive days. One group received ungraded exposure (N = 25), beginning with the most feared items from avoidance hierarchies. Another group received graded exposure (N = 23), beginning with the least feared hierarchy items. Approximately one-third of this severely agoraphobic sample was housed in an initial assessment. At posttreatment and 6 months later, the conditions proved to be equally effective (although, intriguingly, the graded group reported the treatment to be more distressing). However, ungraded exposure was clearly superior at the 5-year follow-up assessment: 76% of the intensive group versus 35% of the graded group reported themselves to be completely free of symptoms. When 104 subjects were added to the intensive exposure format, the same results were obtained. Of 129 subjects, 78% were reported completely symptom-free 5 years later. This dramatic set of results suggests that an intensive approach, which is likely to produce higher levels of arousal than a graduated approach, can be very beneficial (at least when conducted in a massed format). Unfortunately, the validity of the outcome measures in this study is somewhat questionable, and replication by independent investigators has yet to be reported.

The amount of time devoted to in vivo exposure is very dependent on the patient's agoraphobia profile. Obviously, more time is needed for patients with more severe agoraphobia.

**Interoceptive Exposure**

In interoceptive exposure, the goal is deliberately to induce feared physical sensations a sufficient number of
times, and long enough each time, so that misappraisals about the sensations are disconfirmed and conditional anxiety responses are extinguished. A standard list of exercises, such as hyperventilating and spinning, is used to establish a hierarchy of interoceptive exposures. With a graduated approach, exposure begins with the less distressing physical exercises and continues with the more distressing exercises. It is essential that the patient endure the sensations beyond the point at which they are first noticed, for at least 30 seconds to 1 minute, because early termination of the task may eliminate the opportunity to learn that the sensations are not harmful and that the anxiety can be tolerated. The exercise is followed by a discussion of what the patient learned about the physical sensations. These interoceptive exercises are practiced daily outside of the therapy session to consolidate the process of learning. Interoceptive exposure extends to naturalistic activities that induce somatic sensations (e.g., caffeine consumption, exercise).

A series of studies reported on the effects of interoceptive exposure independent of other therapeutic strategies. Early on, Bohn, Harrison, and Rees (1971) and Haslam (1974) observed successful reduction in reactivity with repeated infusions of sodium lactate (a drug that produces panic-type bodily sensations). However, panic was not monitored in these investigations. Griez and van den Houw (1986) compared six sessions of graduated CO₂ inhalations to a treatment regimen of propranolol (a beta-blocker chosen because it suppresses symptoms induced by CO₂ inhalations), both conducted over the course of 2 weeks. CO₂ inhalation treatment resulted in a mean reduction from 12 to four panic attacks, which was superior to the results from propranolol. In addition, inhalation treatment resulted in significantly greater reductions in reported fear of sensations. A 6-month follow-up assessment suggested maintenance of treatment gains, although panic frequency was not reported. Beck and Shipherd (1997) similarly found a positive effect of repeated CO₂ inhalations, although it had little effect on agoraphobia (Beck, Shipherd, & Zebb, 1997). Broocks and colleagues (1998) tested the effects of exercise (with once-weekly supportive contact) in comparison to clomipramine or drug placebo over 10 weeks. The exercise group was trained to run 4 miles, three times per week. Despite high attrition from exercise (31%), exercise was more effective than the drug placebo condition. However, clomipramine was superior to exercise.

In the first comparison to other cognitive and behavioral treatments, Barlow and colleagues (1989) compared applied PMR, interoceptive exposure plus breathing retraining and cognitive restructuring, their combination with applied PMR, and a waiting-list control, in a sample with panic disorder with limited agoraphobia. The two conditions involving interoceptive exposure, breathing retraining and cognitive restructuring, were significantly superior to applied PMR and wait-list conditions. The results were maintained 24 months following treatment completion for the group receiving interoceptive exposure, breathing retraining and cognitive restructuring without PMR, whereas the combined group tended to deteriorate over follow-up (Craske, Brown, & Barlow, 1991). As already mentioned, we compared interoceptive exposure, cognitive therapy, and in vivo exposure to breathing retraining, cognitive therapy, and in vivo exposure for individuals with varying levels of agoraphobia. The condition that included interoceptive exposure was slightly superior to breathing retraining at posttreatment and 6 months later (Craske et al., 1997). Similarly, Ito, Norhiroma, Basgdl, and Marks (1996) found a trend for those who added interoceptive exposure to their self-directed in vivo exposure and breathing retraining to be more likely to achieve at least a 50% improvement in phobic fear and avoidance. However, the combination of breathing education, breathing retraining, and repeated interoceptive exposure to hyperventilation did not increase the effectiveness of in vivo exposure for agoraphobia (de Beurs, Lang, van Dyck, & Koele, 1995).

Interoceptive exposure is now a standard component of cognitive-behavioral therapy for panic disorder (e.g., Barlow et al., 2000; Craske, Lang, Akins, & Myskowski, 2005), although different groups give different emphases to interoceptive exposure, with some emphasizing it as a means for extinguishing fear responses (Barlow & Craske, 2006) and others, as a vehicle for disconfirming misappraisals (Clark, 1996).

Optimizing Learning during Exposure

Our understanding of the mechanisms of exposure therapy has evolved over time. One of the most influential theories is emotional processing theory, which emphasized habituation of fear responding within an exposure trial as a necessary precursor to habituation across treatment sessions, that in turn leads to long-term corrective learning (Foos & Kozak, 1988; Foos & McNally, 1996). Most recently, we have emphasized
optimizing inhibitory learning and its retrieval in ways that are not necessarily dependent on reductions in fear throughout trials of exposure (Craske et al., 2008); we discuss this approach below.

Emotional processing theory emphasizes mechanisms of habituation as precursors to cognitive correction. Specifically, emotional processing theory purports that the effects of exposure therapy derive from activation of a "fear structure" and integration of information that is incompatible with it, resulting in the development of a non-fear structure that replaces or competes with the original one. Incompatible information derives first from within-session habituation, or reduction in fear responding with prolonged exposure to the fear stimulus. Within-session habituation is seen as a prerequisite for the second piece of incompatible information, which derives from between-session habituation over repeated occasions of exposure. Between-session habituation is purported to form the basis for long-term learning and to be mediated by changes in "meaning," or lowered probability of harm (i.e., risk) and lessened negativity (i.e., valence) of the stimulus. Emotional processing theory guides clinicians to focus on the initial elevation of fear followed by within- and between-session reductions in fear as signs of treatment success. Although enticing in its face validity, support for the theory has been inconsistent at best (Craske et al., 2008; Craske, Liao, Brown, & Vervliet, 2012). Rather, the evidence suggests that the amount by which fear habituates from the beginning to the end of an exposure practice is not a good predictor of overall outcomes, and that evidence for between-session habituation is mixed (Craske et al., 2008, 2012).

A return to the science of fear learning and extinction may help to explain the effects of exposure therapy and thereby optimize its implementation. It is now thought that inhibitory learning is central to extinction (Bouton, 1993). Inhibitory pathways are also recognized in the neurobiology of fear extinction (see Sotres-Bayon, Cain, & LeDoux, 2006). Within a Pavlovian conditioning approach, inhibitory learning means that the original conditioned stimulus-uncorrelated stimulus (CS-US) association learned during fear conditioning is not erased during extinction, but rather is left intact as a new, secondary learning about the CS-US develops (Bouton, 1993). The degree to which inhibitory associations shape fear responding at retest (the index of strength and stability of new "learning") is independent of fear levels expressed throughout extinction and instead is dependent on factors such as context and time.

Based on the inhibitory retrieval model of extinction, outcomes may be enhanced by strategies that do not rely on fear reduction within a trial of exposure (Craske et al., 2008, 2012). Indeed, fear reduction may become a safety behavior for persons with panic disorder (since fear reduction eradicates the very thing that is feared), such that a more appropriate goal may be to maintain high levels of fear and anxiety in order to disconfirm the expectancy of negative consequences. One translational possibility is "deepened extinction" (Rescorla, 2006), in which multiple fear conditional stimuli are first extinguished separately before being combined during extinction, and in animal studies, decrease spontaneous recovery and reinstatement of fear. Indeed, this is what is essentially done when interoceptive exposure is conducted in feared agoraphobic situations (Barlow & Craske, 1994) and recent experimental data supports the beneficial effects of deepened extinction in human conditioning studies (Culver, Vervliet, & Craske, in press).

In addition, the effects of exposure therapy may be enhanced by the prevention or removal of "safety signals" or "safety behaviors." Common safety signals and behaviors for clients with panic disorder are the presence of another person, therapists, medications, or food or drink. In the experimental literature, safety signals alleviate distress in the short term, but when they are no longer present, the fear returns (Lovibond, Davis, & O'Flaherty, 2000), an effect that may derive in part from interference with the development of inhibitory associations. In phobic samples, the availability and use of safety signals and behaviors has been shown to be detrimental to exposure therapy (Sloan & Telch, 2002), whereas instructions to refrain from using safety behaviors improved outcomes (Salkovskis, 1991). Similarly, the use of safety signals was associated with poorer outcomes for panic (Helbig-Lang & Petermann, 2010). However, recent data have presented contradictory findings (Rachman, Shafran, Radomsky, & Zysk, 2011).

Further options include stimulus variability throughout exposure, since variability has been shown to enhance the storage capacity of newly learned information. Two studies with clinical analogues have demonstrated positive benefits in terms of spontaneous recovery (Lang & Craske, 2000; Rowe & Craske, 1998), while a third showed trends only (Kiroumi et al., 2011). In the treatment for panic disorder with agoraphobia, this implies conducting exposure for varying durations, at varying levels of intensity, rather than
continuing exposure in one situation until fear declines before moving to the next situation. Notably, such variability typically elicits higher levels of anxiety during exposure, but without detrimental effects and sometimes with beneficial effects in the long term.

Based on evidence for fear extinction to be weakened by antagonists of the glutamate receptors in the amygdala, Walker and Davis (2002) tested and demonstrated that drug agonists of the same receptors, and in particular, D-cycloserine, enhance extinction in animal studies. In a meta-analysis of the efficacy of D-cycloserine for anxiety disorders. Norberg, Krystal, and Tobin (2008) reported effect sizes of $d = 0.60$ at posttreatment and 0.47 at follow-up in clinical anxiety samples. D-Cycloserine in combination with interoceptive exposure for panic clients has resulted in a greater reduction in symptom severity, and a greater likelihood of achieving a change in clinical status at posttreatment and 1-month follow-up compared to exposure plus placebo (Oto et al., 2010). Notably, D-cycloserine has been shown to have positive effects without influencing the level of fear during exposure per se.

A number of options for enhancing retrieval of the extinction memory have been tested. One option during extinction training is to include retrieval cues to be used in other contexts once extinction is over. This has been shown to be effective in animal studies and human conditioning studies (see Craske et al., 2012, for a review). In clinical analogue samples, the effects of a retrieval cue upon context renewal were very weak in one study (Cliber et al., 2012), although instructions to reinstate what was learned mentally during exposure had more robust effects in reducing context renewal in another study (Mystkowski, Craske, Echiverri, & Lautus, 2006). In the treatment of panic disorder, this approach simply suggests that clients carry with them cues (e.g., wristband) to remind them what they learned during exposure therapy (as long as the cues do not become safety signals), or are prompted to remind themselves of what they learned in exposure therapy each time they experience previously feared sensations or situations.

Another option is to provide multiple contexts in which extinction takes place. This approach has been shown to offset context renewal in rodent samples, and in a clinical analogue study of exposure therapy (Vansteenwegen et al., 2007) although the results are not always consistent (Neumann, Lipp & Cory, 2007). In the treatment of panic disorder and agoraphobia, this would mean asking clients to conduct their interoceptive and in vivo exposures in multiple different contexts, such as when alone, in unfamiliar places, or at varying times of day or varying days of the week.

A recent (re-)discovery is that retrieving already stored memories induces a process of reconsolidation (Nader, Schafe, & Le Doux, 2000), since the memory is written into long-term memory again, requiring de novo neurochemical processes. Thus, it may be possible to change memories during the reconsolidation time frame upon retrieval. Propranolol, a beta-blocker, has been shown to block the reconsolidation of memories, and Debiec and Le Doux (2004) found that infusions of propranolol blocked the reconsolidation of a previously formed CS-US memory, and led to the erasure of the fear response and resistance to reinstatement effects. This suggests that propranolol upon retrieval may be a useful clinical tool, and indeed, two fear conditioning studies in healthy humans (Kindt, Soeter, & Vervliet, 2009; Soeter & Kindt, 2010) have replicated the effects. However, the effects have not been tested in the context of exposure therapy for panic disorder.

Role of Acceptance during Exposure

Cognitive and somatic coping skills are central to cognitive-behavioral therapy and are taught to facilitate and improve exposure therapy. Newer approaches that explore acceptance and cognitive defusion (e.g., acceptance and commitment therapy; Hayes, Strosahl, & Wilson, 1999) have been gaining interest, especially given evidence that experiential avoidance is a correlate of anxious psychopathology and acceptance increases willingness to experience and lessens emotional distress over induced anxiety symptoms in individuals with panic disorder (e.g., Campbell-Sills et al., 2006; Eifert & Helfer, 2003), including CO$_2$ inhalation challenges (Levitt et al., 2004). Interestingly, the acceptance approach is entirely consistent with our formulation of interoceptive exposure, in which patients are encouraged to experience the feared physical sensations without any attempt to lessen them or to think differently about them in the moment of exposure. We recently extended this model of acceptance during interoceptive exposure to acceptance during in vivo exposure in an open trial of 11 patients with panic disorder (Meuret, Tsehig, Rosenfeld, Hayes, & Craske, 2012). In general, the exposures were an opportunity for patients to behave with their panic-related thoughts, feelings, and bodily sensations; in other words, patients were encouraged to realize that they can drive for and reach life goals, even in the presence of unpleasant inner experiences. To that
end, it was explicitly stated that the level of anxiety or fear was not the determining factor. Rather, it was explained that “willingness can do surprising things to one’s inner experiences. If one is willing to experience anxiety it may or may not show up. Thus, we are not going to judge the success of these exposures on the anxiety level the patient has, but instead in how open you are to what might show up.” To plan effectively for interoceptive (i.e., eliciting panic sensations such as a racing heart or shortness of breath) and in vivo exposures (i.e., seeking places and situations that one previously avoided because of the fear of panic sensations), a hierarchy of least to most anxiety-provoking items was created. Movement up the hierarchy was not based on reductions in anxiety at the preceding step but high willingness to experience panic-related inner experiences. During the exposures, patients were encouraged to maintain an open, nonjudgmental stance toward whatever thoughts, feelings, and bodily sensations arose in a given moment, experiencing them for what they were, and moving toward them while anxious. Treatment was associated with clinically significant improvements in panic symptom severity, willingness to allow inner experiences to occur, and reductions in avoidant behavior. In another study of a mixed anxiety disorder sample, we found very few differences in outcome between acceptance and commitment therapy (Hayes et al., 1999) and cognitive-behavioral therapy, although the treatments were matched on amount of time spent on exposure therapy, albeit framed differently within each condition (Arch et al., 2012). Thus, the data to date suggest that both a cognitive therapy coping approach and an acceptance-based exposure approach are effective.

OVERALL EFFICACY OF COGNITIVE-BEHAVIORAL THERAPY

An extensive body of research has evaluated the efficacy of cognitive-behavioral therapy for panic disorder and agoraphobia. Cognitive-behavioral therapy, involving most or all of the components just listed, yields panic-free rates in the range of 70–80% and high end-state rates (i.e., within normative ranges of functioning) in the range of 50–70% for panic disorder with minimal agoraphobia (e.g., Barlow et al., 1989; Clark et al., 1994). Although agoraphobic avoidance is sometimes associated with less positive response (e.g., Dow et al., 2007), the overall within-group effect size for change in panic disorder and agoraphobia from pre- to post-treatment is very large (e.g., effect size = 1.53; Norton & Price, 2007). Moreover, the between-group effect size is substantial in comparison to wait-list conditions (e.g., effect size = 0.64; Hays, Donnelly, Corry, & Vas, 2006). However, more research is needed comparing cognitive-behavioral therapy to alternative active treatment conditions.

The effectiveness extends to clients who experience nocturnal panic attacks (Craske, Lang et al., 2005). Furthermore, cognitive-behavioral therapy results in improvements in rates of comorbid anxiety and mood disorders (e.g., Craske et al., 2007; Tsao, Mystkowski, Zucker, & Craske, 2005), although one study suggested that the benefits for comorbid conditions may lessen over time, when assessed 2 years later (Brown et al., 1995). Finally, applications of cognitive-behavioral therapy lower relapse rates upon discontinuation of high-potency benzodiazepines (e.g., Spiegel, Bruce, Gregg, & Nazzarelli, 1994). The effects of cognitive-behavioral therapy are sustained over time, as meta-analyses show little change (i.e., maintenance of treatment effects) from posttreatment to follow-up (effect size = 0.12; Norton & Price, 2007). From their review of meta-analyses for cognitive behavioral therapy across all disorders, Butler, Chapman, Forman, and Beck (2006) concluded that evidence for maintenance of treatment gains was particularly strong for panic disorder, where the rate of relapse was almost half the rate of relapse following pharmacotherapy. Continuing improvement after acute treatment is facilitated by involvement of significant others in every aspect of treatment for agoraphobia (e.g., Cerny et al., 1987). Also, booster sessions enhance long-term outcomes (Craske et al., 2006).

Efficacy data from research settings are now being complemented by effectiveness data from real-world, primary care settings. In a randomized controlled trial in primary care settings with novice therapists, cognitive-behavioral therapy combined with expert recommendations for medication regimens was more effective than treatment as usual (Roy-Byrne, Craske, et al., 2005). The effects appeared primarily to be due to cognitive-behavioral therapy rather than medication (Craske, Golinelli, et al., 2008). In the more recent CALM study (Craske et al., 2011), the effectiveness of cognitive-behavioral therapy for panic disorder in primary care settings was demonstrated in the hands of nonexperienced therapists with the aid of a computerized guide, combined with expert recommendations for medication, relative to treatment as usual.