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Panic Disorder and Agoraphobia

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Overview

The current diagnostic criteria for panic disorder, according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV, American Psychiatric Association, 1994), are comprised of recurrent unexpected panic attacks, and anxiety about future panic attacks or their consequences, or a significant behavioral change because of the panic attacks. The additional anxiety about panic, combined with catastrophic cognitions about panic sensations, contributes to the differentiation between the person with panic disorder and the person with occasional panic attacks (e.g., Telch, Lucas, and Nelson, 1989). Agoraphobia refers to avoidance or endurance with dread of situations from which escape might be difficult or help unavailable in the event of a panic attack, or in the event of developing symptoms that could be incapacitating and embarrassing, such as loss of bowel control or vomiting. Typical agoraphobic situations include shopping malls, waiting in line, movie theaters, traveling by car or bus, crowded restaurants, and being alone.

In the general population, the 12-month prevalence estimate for panic disorder across the United States and several European countries is about 2% in adults and adolescents (Goodwin, Fergusson, and Horwood, 2005; Kessler *et al.*, 2005b). 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). Across all studies, females are more frequently affected than males at a rate of approximately 2 : 1 (Kessler *et al.*, 2005b). Although panic attacks occur in children, the overall prevalence of panic disorder is low prior to 14 years of age (<0.4%) (Craske *et al.*, 2010). The rates of panic disorder show a gradual increase during adolescence, particularly in girls, and possibly following the onset of puberty (Craske *et al.*, 2010). The modal age of onset is late teenage years and early adulthood (Kessler *et al.*, 2005a), although treatment is usually sought at a much later age, around 34 years (e.g., Noyes *et al.*, 1986). The

prevalence rates decline in older individuals, possibly reflecting diminishing severity to subclinical levels (Wolitzky-Taylor *et al.*, 2010). In general, differences in prevalence across gender, culture, and age groups may be due to a variety of factors, including the expression of the disorder, underlying physiology or biology, varying degrees of concern about the dangerousness of symptoms of autonomic arousal and mental symptoms of anxiety, and sensitivity of instrumentation for diagnosing panic disorder.

Panic disorder and agoraphobia tend to be chronic conditions, with severe financial and interpersonal costs; that is, only a minority (30%) of untreated individuals remit without subsequent relapse, although a similar number experience notable improvement, albeit with a waxing and waning course (35%) (Katschnig and Amering, 1998; Roy-Byrne and Cowley, 1995). Also, panic disorder is associated with high levels of social, occupational, and physical disability, considerable economic costs, and the highest number of medical visits among the anxiety disorders, although the effects are strongest with the presence of agoraphobia (Wittchen *et al.*, 2010).

Rarely does the diagnosis of panic disorder, with or without agoraphobia, occur in isolation. Commonly co-occurring Axis I conditions include specific phobias, social phobia, dysthymia, generalized anxiety disorder, major depressive disorder, and substance abuse (e.g., Brown *et al.*, 2001; Kessler *et al.*, 2005b). Also, from 25 to 60% of persons with panic disorder also meet criteria for a personality disorder, mostly avoidant and dependent personality disorders (e.g., Chambless and Renneberg, 1988). However, the nature of the relationship between panic disorder/agoraphobia and personality disorders remains unclear, especially as some “personality disorders” remit after successful treatment of panic disorder/agoraphobia (e.g., Latas *et al.*, 2000; Marchesi *et al.*, 2005; Ozkan and Altindag, 2005).

Cognitive Behavioral Model

Several independent lines of research (Barlow, 1988; Clark, 1986; Ehlers and Margraf, 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 (i.e., temperament, such as negative affectivity) and biological (i.e., genetic) predispositions are believed to enhance the vulnerability to acquire such fear. 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.

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 is “negative affect,” or the tendency to experience a variety of negative emotions across a variety of situations, even in the absence of objective stressors (Watson and Clark, 1984). Neuroticism predicts the onset of panic attacks in adolescents (Hayward *et al.*, 2000; Schmidt, Lerew and 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 *et al.*, 2001). Numerous multivariate genetic analyses of human twin samples consistently

attribute approximately 30–50% of variance in neuroticism to additive genetic factors (Eley, 2001; Lake *et al.*, 2000). In addition, anxiety and depression appear to be variable expressions of the heritable tendency toward neuroticism (Kendler *et al.*, 1987). Symptoms of panic (i.e., breathlessness and 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 *et al.*, 1988).

Another temperament is anxiety sensitivity, which refers to the trait of believing that anxiety and 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, especially the physical concerns subscale (Zinbarg, Barlow, and Brown, 1997). Anxiety sensitivity is believed to comprise a specific psychological vulnerability for panic disorder because it primes fear reactivity to bodily sensations. In support, 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 and Reiss, 1992), and community samples with specific phobias or no anxiety disorders (Ehlers, 1995). 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 controlling for history of panic attacks and trait anxiety (Schmidt, Lerew and Jackson, 1999). Finally, panic attacks themselves elevate anxiety sensitivity over a 5-week period in adults (Schmidt Lerew, and Jackson, 1999), and over a 1-year period in adolescents, albeit to a lesser extent (Weems *et al.*, 2002).

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

Acute “fear of fear” (or more accurately, anxiety focused on somatic sensations) that develops after initial panic attacks is attributed to two factors: catastrophic misappraisals of bodily sensations (i.e., misinterpretation of sensations as signs of imminent death, loss of control, and so on) (Clark, 1986); and interoceptive conditioning, or conditioned 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 bodily sensations of arousal coming to serve as conditional stimuli that trigger increased autonomic arousal and fear through Pavlovian conditioning (Bouton, Mineka, and Barlow, 2001). Thus, small changes in physiological functioning lead to conditioned fear or panic as a result of prior pairings of these initial somatic sensations with full-blown panic attacks. An extensive experimental literature attests to the robustness of interoceptive conditioning (e.g., Dworkin and Dworkin, 1999), particularly with regard to early interoceptive drug onset cues becoming conditioned stimuli for larger drug effects (e.g., Sokolowska, Siegel, and Kim, 2002). In addition, interoceptive conditioned responses are not dependent on

conscious awareness of triggering cues and thus have been observed under anesthesia (e.g., Block *et al.*, 1987). As such, interoceptive conditioning accounts for what appear to be “out of the blue” panic attacks.

Evidence for extreme fear and anxiety of somatic sensations is robust across a variety of paradigms. Persons with panic disorder endorse strong beliefs that bodily sensations associated with panic attacks cause physical or mental harm (e.g., McNally and Lorenz, 1987). They are more likely to interpret bodily sensations in a catastrophic fashion (Clark *et al.*, 1988), and to allocate more attentional resources to words that represent physical threat such as “disease” and “fatality” (e.g., Hope *et al.*, 1990), catastrophe words, such as “death” and “insane” (e.g., Maidenberg *et al.*, 1996), and heartbeat stimuli (Kroeze and van den Hout, 2000). Also, individuals with panic disorder show enhanced brain potentials to panic-related words (Pauli *et al.*, 2005). In addition, they are more likely to become anxious in procedures that elicit bodily sensations similar to the ones experienced during panic attacks, including benign cardiovascular, respiratory, and audiovestibular exercises (Antony *et al.*, 2006), as well as more invasive procedures such as carbon dioxide inhalations, compared to clients with other anxiety disorders (e.g., Perna *et al.*, 1995; Rapee *et al.*, 1992) or healthy controls (e.g., Gorman *et al.*, 1994). The findings are not fully consistent, however, as clients with panic disorder did not differ from clients with social phobia in response to an epinephrine challenge (Veltman *et al.*, 1996). Nonetheless, individuals with panic disorder also fear signals that ostensibly reflect heightened arousal and false physiological feedback (Craske *et al.*, 2002; Ehlers *et al.*, 1988).

Such anxiety about bodily sensations plays a central role in the perpetuation of panic disorder. First, once the bodily sensations are noticed, they elicit fear in an individual with panic disorder. This fear serves to intensify the sensations, causing an increase in fear, which further enhances the bodily sensations in a self-perpetuating cycle of fear and bodily sensations that typically results in a panic attack. 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 that generates even further distress (Craske, Glover, and DeCola, 1995). Third, the perceived uncontrollability, or inability to escape from, or terminate bodily sensations again is likely to generate heightened anxiety (e.g., Maier, Laudenslager, and Ryan, 1985). 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. 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 by increasing attentional vigilance for these bodily cues. Thus, a maintaining cycle of panic and anxious apprehension develops.

Individuals with panic disorder often engage in safety behaviors that they believe enable them to escape or avoid the feared outcome. For example, if individuals believe that they will pass out during a panic attack, they might sit down or hold on to an object for support. Engaging in safety behaviors prevents disconfirmation of cognitive misappraisals, thus contributing to the maintenance of panic disorder (Salkovskis, Clark, and Gelder, 1996). Individuals may also engage in safety behaviors designed to prevent panic, or its feared consequences, such as carrying around anxiolytic medication

or traveling with a companion who makes them feel safe. Another panic-maintaining behavioral response is overt avoidance of particular places or situations where panic attacks are anticipated to occur. Avoidance prevents disconfirmation of catastrophic misappraisals, and reinforces the fear that those particular situations are dangerous, increasing the likelihood of panicking in those situations in the future.

Components of Cognitive Behavioral Therapy

As outlined in more detail elsewhere (Simos, 2002), the treatment begins with education about the nature of panic, the causes of panic and anxiety, and the way in which 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 common myths and misconceptions about panic symptoms (i.e., beliefs about going crazy, dying, or losing control).

Self-monitoring is introduced in the first treatment session and is continued throughout the entire treatment. Self-monitoring functions in two ways: to provide ongoing assessment of change in panic, anxiety, and avoidance; and as a therapeutic tool to encourage objective self-awareness and increase accuracy in self-observation. Clients are asked to keep at least two types of self-monitoring records. The first is a panic attack record, to be completed as soon as possible after each panic attack; this record provides a description of cues, maximal distress, symptoms, thoughts, and behaviors. The second is a daily mood record, completed at the end of each day, to keep record of overall or average levels of anxiety, depression, and so on. Additionally, clients may keep a daily record of activities or situations avoided.

Breathing retraining is a commonly used somatic coping skill, given evidence for respiratory abnormalities in panic disorder possibly due to hypersensitive medullary carbon dioxide (CO_2) detectors, resulting in hypocapnia (i.e., lower than normal levels of $p\text{CO}_2$) (e.g., Caldirola *et al.*, 2004). Traditional breathing retraining involves slow, abdominal breathing exercises. However, its value has been questioned in terms of the degree to which it actually corrects hypocapnic breathing or rather serves as a distraction (Garssen, de Ruiter, and van Dyck, 1992). In contrast to traditional breathing retraining, capnometry-assisted respiratory training (CART) (Meuret *et al.*, 2008) uses immediate feedback of end-tidal $p\text{CO}_2$ to teach clients how to raise their subnormal levels of $p\text{CO}_2$ (hyperventilation) and thereby gain control over dysfunctional respiratory patterns and associated panic symptoms (e.g., shortness of breath and dizziness). CART has been shown to improve panic symptoms, in part through reducing hypocapnic breathing (Meuret *et al.*, 2010). Another somatic coping skill is progressive muscle relaxation, in which clients are trained over a number of weeks in 16-muscle groups, 8-muscle groups, 4-muscle groups, and finally cue-control relaxation, at which point relaxation is used as a coping skill for practicing exposure to items from a hierarchy of anxiety-provoking tasks.

In the cognitive restructuring component of cognitive behavioral therapy (CBT), detailed self-monitoring of emotions and associated cognitions is used to identify

specific beliefs, appraisals, and assumptions. Relevant cognitions are categorized into types of errors, such as overestimations of risk of negative events, or catastrophizing the meaning of events. In labeling the type of cognitive distortion, the client is encouraged to use an empirical approach to examine the validity of thoughts by considering all of the available evidence. Therapists use Socratic questioning to help clients make guided discoveries and question their anxious thoughts. Next, alternative hypotheses are generated that are more evidence-based. In addition to surface-level appraisals (such as “my heart is racing dangerously too fast”), core-level beliefs or schemata (such as “I am too weak to withstand distress”) are questioned in the same way.

In vivo exposure refers to repeated and systematic real-life exposure to agoraphobic situations. 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, although there is some evidence to suggest that intensive or ungraduated exposure may be effective (e.g., Feigenbaum, 1988). Critical to *in vivo* exposure is the removal of safety signals and safety behaviors, such as other people, empty or full medication bottles, seeking reassurance, or checking for exits. Reliance on safety signals and safety behaviors attenuates distress in the short term but is believed to maintain excessive anxiety in the long term. They are replaced by effective use of cognitive restructuring and somatic coping skills, with care to ensure that the coping skills themselves do not become alternative safety behaviors. *In vivo* exposure can be conducted with the therapist’s guidance, followed by self-directed exposures between sessions (to enhance generalization of learning and to limit the safety signal value of the therapist). Recent data support the value of therapist-directed exposure (Gloster *et al.*, 2011).

In interoceptive exposure, the goal is to deliberately induce feared physical sensations a sufficient number of times and for long enough each time so that misappraisals about the sensations are disconfirmed and conditioned anxiety responding extinguishes. A standard list of exercises, such as hyperventilating and spinning, are used to establish a hierarchy of interoceptive exposures. Clients are encouraged to endure the sensations beyond the point at which they are first noticed because early termination interferes with new learning. Interoceptive exposure is usually first conducted in-session with the therapist’s guidance, followed by self-directed practice between sessions. Interoceptive exposure extends to naturalistic activities that inherently induce somatic sensations (e.g., caffeine consumption and exercise programs). Eventually, *in vivo* exposure is combined with interoceptive exposure, by deliberately inducing feared sensations in feared situations.

A final step of CBT is relapse prevention, in which clients are informed that recurrences of panic, anxiety or avoidance behavior are likely to occur in the future. They are encouraged to view such recurrences as lapses rather than failure, and to reapply their coping skills and reinstitute their practice of interoceptive and *in vivo* exposure.

Science of Exposure Therapy

Exposure therapy has developed over time, originating with graduated imaginal exposure combined with counterconditioning through relaxation (i.e., systematic desensitization) developed by Wolpe (1959). Emotional processing theory emphasized

habituation of fear responding within an exposure trial as a necessary precursor to habituation across treatment sessions, with the aim of long-term corrective learning (Foa and Kozak, 1986; Foa and 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 nonfear 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, 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, and LeDoux, 2006). Within a Pavlovian conditioning approach, inhibitory learning means that the original association between the conditional stimulus (i.e., the neutral stimulus that is paired with an innately aversive stimulus) and the unconditional stimulus (the innately aversive stimulus) learned during fear conditioning is not erased during extinction, but rather is left intact as a new, secondary learning (i.e., the conditional stimulus no longer predicts the unconditional stimulus) 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), where multiple fear conditional stimuli are first extinguished separately before being combined during extinction, and in animal studies, decreases spontaneous recovery and reinstatement of fear. Indeed, this is what

is essentially done when interoceptive exposure is conducted in feared agoraphobic situations (Barlow and Craske, 1994) and recent experimental data support the beneficial effects of deepened extinction in human conditioning studies (N.C. Culver, B. Vervliet, and M.G. Craske, manuscript in preparation).

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, and 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 and Telch, 2002), whereas instructions to refrain from using safety behaviors improved outcomes (Salkovskis, 1991), although recent data have presented contradictory findings (Rachman *et al.*, 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 analogs have demonstrated positive benefits in terms of spontaneous recovery (Lang and Craske, 2000; Rowe and Craske, 1998), while a third showed trends only (Kircanski *et al.*, 2012). In the treatment for panic disorder/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 *et al.* (2002) tested and demonstrated that drug agonists of the same receptors, and in particular, D-cycloserine, enhanced extinction in animal studies. In a meta-analysis of the efficacy of D-cycloserine for anxiety disorders, Norberg, Krystal, and Tolin (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 (Otto *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 is to include retrieval cues during extinction training 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 analog samples, the effects of a retrieval cue upon context renewal were very weak in one study (Culver, Stoyanova, and Craske, 2011), although instructions to mentally reinstate what was learned during exposure had more robust effects in reducing context renewal in another study (Mystkowski *et al.*, 2006). In the treatment of panic disorder, this approach simply suggests that clients carry cues (e.g., wrist band) with them to remind them of 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 analog study of exposure therapy (Vansteenwegen *et al.*, 2007), although the results are not always consistent (Neumann, Lipp, and 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 the day or varying days of the week.

A recent (re-)discovery is that retrieving already stored memories induces a process of reconsolidation (Nader, Schafe, and 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 β -blocker, has been shown to block the reconsolidation of memories, and Debiec and Ledoux (2004) found that infusions of propranolol blocked the reconsolidation of a previously formed CS-US memory, and led to 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, and Vervliet, 2009; Soeter and Kindt, 2010) have replicated the effects. However, the effects have not been tested in the context of exposure therapy for panic disorder.

Differential Diagnosis

Panic disorder is not diagnosed if the panic attacks are judged to be a direct physiological consequence of a general medical condition, in which case an anxiety disorder due to a general medical condition is diagnosed. Examples of general medical conditions that can cause panic attacks include hyperthyroidism, hyperparathyroidism, pheochromocytoma, vestibular dysfunctions, seizure disorders, and cardiopulmonary conditions (e.g., arrhythmias, supraventricular tachycardia, asthma, and chronic obstructive pulmonary disease) (Fava *et al.*, 2010). Appropriate laboratory tests (e.g., serum calcium levels for hyperparathyroidism) or physical examinations (e.g., for cardiac conditions) may be helpful in determining the etiological role of a general medical condition.

Panic disorder is not diagnosed if the panic attacks are judged to be a direct physiological consequence of a substance (i.e., a drug of abuse and a medication), in which case a substance-induced anxiety disorder is diagnosed. Intoxication with central nervous system stimulants (e.g., cocaine, amphetamines, and caffeine) or cannabis and withdrawal from central nervous system depressants (e.g., alcohol and barbiturates) can precipitate a panic attack. However, if panic attacks continue to occur outside of the context of substance use (e.g., long after the effects of intoxication or withdrawal have ended), a diagnosis of panic disorder should be considered. In addition, because panic disorder may precede substance use in some individuals and may be associated with increased substance use especially for purposes of self-medication, a detailed history should be taken to determine if the individual had panic attacks prior to excessive

substance use. If this is the case, a diagnosis of panic disorder should be considered in addition to a diagnosis of substance dependence or abuse. Features such as onset of panic after the age of 45 or the presence of atypical symptoms during a panic attack (e.g., vertigo, loss of consciousness, loss of bladder or bowel control, slurred speech, or amnesia) suggest that a general medical condition or a substance may be causing the panic attack symptoms.

Panic disorder must be distinguished from other mental disorders (e.g., other anxiety disorders and psychotic disorders) that have panic attacks as an associated feature. By definition, panic disorder is characterized by recurrent, unexpected panic attacks, either initially or later in the course, although expected panic attacks may occur as well. In contrast, panic attacks that occur in the context of other anxiety disorders are always expected (e.g., triggered by social situations in social anxiety disorder, by phobic objects or situations in specific phobia, by worry in generalized anxiety disorder, by obsessions in obsessive-compulsive disorder, or by reminders of the trauma in posttraumatic stress disorder).

The focus of the anxiety also helps to differentiate panic disorder from other disorders associated with panic attacks. In panic disorder, the anxiety is about having more panic attacks or their consequences. In other disorders, the panic attacks are symptoms of anxiety about other issues, such as social evaluation in social anxiety disorder, obsessions in obsessive-compulsive disorder, or traumatic experiences in posttraumatic stress disorder.

Comorbidity

The literature is equivocal as to whether depression has an adverse effect on treatment outcome for panic disorder. Several studies have shown that depression at baseline results in poorer outcomes from CBT for panic disorder/agoraphobia (e.g., Rief *et al.*, 2000; Tsao, Lewin, and Craske, 1998). In contrast, other studies have found that depression does not influence response to CBT for panic disorder (e.g., Allen *et al.*, 2010). As such, questions remain regarding how to manage comorbid depression. Some studies (e.g., Craske *et al.*, 2007) would suggest that no adaptation is necessary because targeted CBT will be equally effective with or without the presence of other disorders. Furthermore, according to these studies, comorbid conditions actually improve following targeted panic disorder treatment. On the other hand, these studies typically exclude the most severe depression or suicidal depression. Others would suggest that depression needs to be addressed, such as through the addition of medication, although empirical support for this supposition is lacking.

To date, few studies include Axis II diagnoses in their diagnostic screening procedures perhaps due to the limited availability of reliable and valid methods of assessment. Of those that do, some suggest that individuals with Axis II features have a poorer response to CBT (Hoffart and Hedley, 1997; Marchand *et al.*, 1998). Other studies show the same rate of improvement, although those with Axis II features start and end at a higher level of severity than those without Axis II features (e.g., van den Hout, Brouwers, and Oomen, 2006). Although there are mixed findings regarding the effect of comorbid personality disorders on treatment outcome, it is necessary

for clinicians to be aware of potential adjustments necessary when working with these clients. For instance, clients may exhibit decreased motivation, especially with regards to exposure and between-session homework. Treatment length may need to be increased to allow such clients to reach the same end-state functioning as their non-comorbid counterparts.

Medical comorbidity, such as cardiac arrhythmias or asthma, may slow improvement rates, given the additional complications involved in discriminating anxiety symptomatology from disease symptomatology, increases in actual medical risk, and the stress of physical diseases. However, the effect of medical comorbidity upon CBT outcome has not been assessed to date, and attempts to modify CBT to address medical comorbidity are only just emerging (Lehrer *et al.*, 2008). When working with medical comorbidity, it is recommended that clinicians work closely with physicians and inquire regarding potential contraindications of exposure to interoceptive and external cues given the specific medical condition. Medical “clearance” prior to the onset of exposure therapy is a good standard of practice but is especially important in working with medical comorbidity. Furthermore, in the context of CBT, it is important to help clients learn to articulate the differences between medical symptoms and nonmedical symptoms, and possibly utilize ongoing monitoring of relevant health indices (e.g., blood pressures or heart rate monitors) during exposure therapy. Cognitively, it is important to engage in problem solving around real medical issues.

With respect to substance use disorders, the majority of research studies exclude individuals with comorbid substance disorder. However, one series of case studies (Lehman, Brown, and Barlow, 1998) found that CBT for panic led to reduced alcohol consumption. In the absence of clear research-based guidelines, it is suggested that clinicians strive to understand which disorder is primary and treat that first; so that if substance disorder is primary, it would be treated first while delaying treatment of the panic disorder (Marshall, 1997). Further research on the effects of comorbidity on treatment is desperately needed given the common co-occurrence of anxiety and substance disorders (e.g., Compton *et al.*, 2007).

Efficacy

An extensive body of research has evaluated the efficacy of CBT for panic disorder with or without agoraphobia (PDA). 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 PDA from pre- to posttreatment is very large, for example, $ES = 1.53$ (Norton and Price, 2007). Moreover, the between-group effect size is substantial in comparison to wait-list conditions, for example, $ES = 0.64$ (Haby *et al.*, 2006). However, more research is needed comparing CBT to alternative active treatment conditions.

The effectiveness extends to clients who experience nocturnal panic attacks (Craske *et al.*, 2005b). Furthermore, CBT results in improvements in rates of comorbid anxiety and mood disorders (e.g., Craske *et al.*, 2007; Tsao *et al.*, 2005), although one study suggests that the benefits for comorbid conditions may lessen over time, when assessed 2 years later (Brown, Antony, and Barlow, 1995). Finally, applications of CBT lower

relapse rates upon discontinuation of high-potency benzodiazepines (e.g., Spiegel *et al.*, 1994).

CBT effects generally are sustained over time as meta-analyses show little change (i.e., maintenance of treatment effects) from posttreatment to follow-up, for example, $ES = 0.12$ (Norton and Price, 2007). From their review of meta-analyses for CBT across all disorders, Butler *et al.* (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, CBT combined with expert recommendations for medication regimens was more effective than treatment as usual (Roy-Byrne *et al.*, 2005). The effects appeared primarily due to CBT (Craske *et al.*, 2005a). In the more recent CALM study (Craske *et al.*, 2011), the effectiveness of CBT 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.

Even though CBT for panic disorder/agoraphobia is efficacious and effective, there is room for improvement. One study estimated that 30% of clients continued to function poorly at follow-up and only 48% reached high end-state status (Brown and Barlow, 1995). In a landmark study (Barlow *et al.*, 2000), only 32% of panic disorder clients assigned to CBT alone demonstrated strong treatment response 12 months after acute treatment. Finally, of those who do start treatment, the mean dropout rate from CBT for panic disorder/agoraphobia is 19%, with a range of 0–54% (Haby *et al.*, 2006).

Medication Management

The combination of CBT (or in some cases behavioral therapy) and antidepressant treatment has shown a small advantage over either CBT alone or antidepressants alone for panic disorder/agoraphobia. A meta-analysis of 21 trials with 1709 clients compared either CBT or antidepressant treatment for panic disorder/agoraphobia to combined CBT-antidepressant treatment (Laberge *et al.*, 1993). Combined treatment was superior to antidepressant pharmacotherapy (RR 1.24, 95% CI 1.02–1.52) or psychotherapy (RR 1.17, 95% CI 1.05–1.31). However, combined treatment resulted in a somewhat greater number of client dropouts due to side effects than psychotherapy alone. The superiority of the combination over either monotherapy appeared to persist as long as the drug was continued. Following discontinuation of the antidepressant, the groups initially assigned to either combined treatment or CBT did better than clients assigned to pharmacotherapy. Similarly, in the landmark study mentioned earlier (Barlow *et al.*, 2000), following medication discontinuation, the combination of medication and CBT fared worse than CBT alone,

suggesting the possibility that state or context-dependent learning in the presence of the medication may have attenuated the new learning that occurs during CBT. For this reason, it is generally recommended that CBT booster sessions be conducted during and following medication withdrawal, although direct empirical testing has not been conducted.

Findings from the combination of high-potency benzodiazepines with behavioral treatments for agoraphobia are limited and mixed (Marks *et al.*, 1993; Wardle *et al.*, 1994). However, several studies reliably show that chronic use of high-potency benzodiazepines for panic disorder/agoraphobia, initiated well before CBT, has detrimental effects on short- and long-term outcomes from CBT, including more attrition, less improvement, and greater likelihood of relapse (e.g., Westra, Stewart, and Conrad, 2002).

Adaptations for Ethnic Subgroups

In general, CBT is aligned with European and North American values of change, self-disclosure, independence and autonomy, and rational thinking – all of which are at odds with values of harmony, family and collectivism, and spirituality that define many other cultures (see Hays and Iwamasa, 2006). Also, cognitive strategies are closely aligned with the European/North American value of rational thinking. As noted by Hays and Iwamasa (2006), emphasis upon cognition, logic, verbal skills and rational thinking can undercut the value of spirituality in many cultures. Related is the emphasis of cognitive strategies upon reductionist cause and effect relations. In contrast, Asian cultural beliefs, for example, emphasize balance (or yin and yang), evaluation of systems holistically, and indirect causes for events. Thus, a client from a different culture may take into account additional causes for events that are not immediately obvious to a North American/European therapist, thereby potentially undercutting the latter's attempts at cognitive restructuring. Another issue is the locus of control, which tends to be more internal than external in Caucasians and more external than internal in many Asian cultures, wherein certain events are judged to be unrelated to one's own actions. In addition, whereas a typical target of CBT is negative self-statements, such self-criticism may be viewed as a motivator to achieve in other cultures, such as Chinese cultures (Hwang and Wood, 2007). Thus, what a therapist may judge to be a "logical outcome" may not coincide with the client's beliefs. Cultural sensitivity of cognitive strategies mandates that therapists become knowledgeable about the client's cultural values and beliefs, something that would be achieved through functional analyses.

To adapt CBT to different cultural groups may mean that exposure therapy goals of independence and autonomy (e.g., being able to drive alone and travel far from home) are cast within, and not at conflict with, cultural values that emphasize family and collectivism. Furthermore, cognitive therapy may be modified for cultures that emphasize balance and indirect causes of events rather than reductionist cause-effect relations. That is, the method by which cognitive restructuring is most effectively implemented may differ across cultures, with Western culture being more suited to single overriding alternative interpretation of a given event and Eastern culture being

more suited to two or more simultaneous explanations that can be invoked depending on the context (Hofmann, 2006).

To make these adaptations requires cultural sensitivity and competency, or having the cultural self-awareness, knowledge, and skills that facilitate the delivery of effective services to ethnically and culturally diverse clients. Frameworks have been proposed for how to adapt CBT to different cultures, such as for Chinese Americans (Hwang, 2006). However, the effectiveness of CBT with diverse clientele is early in its research development, and it is not entirely clear that such adaptation is necessary or beneficial. In the realm of panic disorder, Miranda *et al.* (2005) reviewed evidence in which one study showed that African Americans responded less well to CBT for panic attacks than white Americans, whereas other studies found equivalent treatment outcomes across groups of African American and white Americans.

Summary

Panic disorder and agoraphobia tend to be chronic conditions, often with an unremitting course, considerable social, occupational, and physical disability, and high rates of comorbidity. Evidence supports the conceptualization of panic disorder as an acquired fear of bodily sensations, particularly sensations associated with autonomic arousal. Psychological and biological factors are believed to enhance the vulnerability to acquire such fear. Fear conditioning, avoidant responding, and information processing biases are believed to perpetuate such fear.

Catastrophic misappraisals of bodily sensations during initial panic attacks and interoceptive conditioning lead to acute “fear of fear” (anxiety focused on somatic sensations). Such anxiety about bodily sensations plays a central role in the perpetuation of panic disorder. When bodily sensations are noticed, they elicit fear, and fear intensifies the sensations, causing an increase in fear, which further enhances the bodily sensations in a self-perpetuating cycle of fear and bodily sensations that typically results in a panic attack. Perceived unpredictability and uncontrollability of panic attacks enhances chronic anxious apprehension, which in turn increases the likelihood of panic, by directly increasing the availability of sensations that have become conditioned cues for panic and/or by increasing attentional vigilance for these bodily cues; thus, a maintaining cycle of panic and anxious apprehension develops.

Safety behaviors in which individuals with panic disorder often employ prevent disconfirmation of cognitive misappraisals and contribute to the maintenance of the disorder. Similarly, avoidance of particular places or situations where panic attacks are anticipated to occur prevents disconfirmation of catastrophic misappraisals, and reinforces the fear that those particular situations are dangerous, increasing the likelihood of panicking in those situations in the future.

Formal CBT begins with appropriate psychoeducation about the nature and the causes of panic and anxiety, and the aforementioned vicious cycle of a panic attack. Self-monitoring is introduced early in treatment as it provides ongoing assessment of change in panic, anxiety, and avoidance, and encourages objective self-awareness, and increase accuracy in self-observation. Breathing retraining is a commonly used somatic coping skill, and it involves slow abdominal breathing exercises. In the

cognitive restructuring component of CBT, detailed self-monitoring of emotions and associated cognitions is used to identify specific faulty beliefs, appraisals, and assumptions. Clients are encouraged to use an empirical approach to examine the validity of their cognitions and generate alternative, more evidence-based hypotheses. Repeated and systematic real-life mainly self-directed-exposure to agoraphobic situations is consequently introduced. Interoceptive exposure, repeated exposure to deliberately induced feared physical sensations, is utilized to disconfirm misappraisals of sensations and to extinguish related conditioned anxiety responses. Relapse prevention constitutes the final step of CBT for panic disorder/agoraphobia.

This chapter also discusses psychiatric and medical comorbidity and whether comorbidity could or should influence our standard care, the possible advantages of combined CBT and antidepressant medication treatment, as well as the possible adaptations of CBT for ethnically and culturally diverse clients.

Although CBT is the treatment of choice for panic disorder/agoraphobia, there is ample room for improvement. A substantial number of panic disorder patients drop out from CBT, do not respond adequately, or do not remain panic free after the end of treatment. Cognitive restructuring, breathing retraining as well exposure to feared situations and interoceptive cues comprise CBT. However, which component or which particular subcombination is most critical for outcomes is not clear at this time. Meuret *et al.* (2012) argue that although cognitive skills and breathing retraining are taught to the patient, and consequently are believed to contribute to the final outcome, there is still no way to know whether these skills, apart from being taught, are adopted by the patient and actually implemented during an exposure task. Research on actual adoption of skills within exposure practices may help practitioners manage panic disorder/agoraphobia in a more effective and consistent way.

References

- Allen, L.B., White, K.S., Barlow, D.H. *et al.* (2010) Cognitive-behavior therapy (CBT) for panic disorder: relationship of anxiety and depression comorbidity with treatment outcome. *Journal of Psychopathology and Behavioral Assessment*, 32, 185–192.
- American Psychiatric Association (1994) *Diagnostic and Statistics Manual of Mental Disorders*, American Psychiatric Press, Washington, DC.
- Antony, M.M., Ledley, D.B., Liss, A., and Swinson, R.P. (2006) Responses to symptom induction exercises in panic disorder. *Behavior Research and Therapy*, 44, 85–98.
- Barlow, D.H. (1988) *Anxiety and Its Disorders: The Nature and Treatment of Anxiety and Panic*, Guilford Press, New York.
- Barlow, D.H. and Craske, M.G. (1994) *Mastery of Your Anxiety and Panic II*, Graywind Publications Incorporated, Albany, NY.
- Barlow, D.H., Gorman, J.M., Shear, M.K., and Woods, S.W. (2000) Cognitive-behavioral therapy, imipramine, or their combination for panic disorder: A randomized controlled trial. *Journal of the American Medical Association*, 283 (19), 2529–2536.
- Block, R.I., Ghoneim, M.M., Fowles, D.C. *et al.* (1987) Effects of a subanesthetic concentration of nitrous oxide on establishment, elicitation, and semantic and phonemic generalization of classically conditioned skin conductance responses. *Pharmacology, Biochemistry and Behavior*, 28, 7–14.

- Bouton, M.E. (1993) Context, time and memory retrieval in the interference paradigms of pavlovian learning. *Psychological Bulletin*, 114, 90–99.
- Bouton, M.E., Mineka, S., and Barlow, D.H. (2001) A modern learning-theory perspective on the etiology of panic disorder. *Psychological Review*, 108 (1), 4–32.
- Brown, T.A. and Barlow, D.H. (1995) Long-term outcome in cognitive-behavioral treatment of panic disorder: clinical predictors and alternative strategies for assessment. *Journal of Consulting and Clinical Psychology*, 63, 754–765.
- Brown, T.A., Antony, M.M., and Barlow, D.H. (1995) Diagnostic comorbidity in panic disorder: effect on treatment outcome and course of comorbid diagnoses following treatment. *Journal of Consulting and Clinical Psychology*, 63, 408–418.
- Brown, T.A., Campbell, L.A., Lehman, C.L. *et al.* (2001) Current and lifetime comorbidity of the DSM-IV anxiety and mood disorders in a large clinical sample. *Journal of Abnormal Psychology*, 110 (4), 585–599.
- Butler, A., Chapman, J., Forman, E., and Beck, A. (2006) The empirical status of cognitive-behavioral therapy: a review of meta-analyses. *Clinical Psychology Review*, 26, 17–31.
- Caldirola, D., Bellodi, L., Caumo, A. *et al.* (2004) Approximate entropy of respiratory patterns in panic disorder. *American Journal of Psychiatry*, 161, 79–87.
- Cerny, J.A., Barlow, D.H., Craske, M.G., and Himadi, W.G. (1987) Couples treatment of agoraphobia: a two-year follow-up. *Behavior Therapy*, 18, 401–415.
- Chambless, D.L. and Renneberg, B. (1988) Personality disorders of agoraphobics. Paper presented at World Congress of Behavior Therapy, Edinburgh, Scotland.
- Clark, D.M. (1986) A cognitive approach to panic. *Behaviour Research and Therapy*, 24, 461–470.
- Clark, D.M., Salkovskis, P., Gelder, M. *et al.* (1988) Tests of a cognitive theory of panic, in *Panic and Phobias II* (eds I. Hand and H. Wittchen), Springer, Berlin.
- Compton, W.M., Thomas, Y.F., Stinson, F.S., and Grant, B.F. (2007) Prevalence, correlates, disability, and comorbidity of DSM-IV drug abuse and dependence in the United States. Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Archives of General Psychiatry*, 64, 566–576.
- Craske, M.G., Glover, D., and DeCola, J. (1995) Predicted versus unpredicted panic attacks: acute versus general distress. *Journal of Abnormal Psychology*, 104, 214–223.
- Craske, M.G., Poulton, R., Tsao, J., and Plotkin, D. (2001) Paths to panic-agoraphobia: an exploratory analysis from age 3–21 in an unselected birth cohort. *Journal of the American Academy of Child and Adolescent Psychiatry*, 40, 556–563.
- Craske, M.G., Lang, A.J., Rowe, M. *et al.* (2002) Presleep attributions about arousal during sleep: nocturnal panic. *Journal of Abnormal Psychology*, 111, 53–62.
- Craske, M.G., Golinelli, D., Stein, M.B. *et al.* (2005a) Does the addition of cognitive behavioral therapy improve panic disorder treatment outcome relative to medication alone in the primary-care setting? *Psychological Medicine*, 35 (11), 1645–1654.
- Craske, M.G., Lang, A.J., Aikins, D., and Mystkowski, J.L. (2005b) Cognitive behavioral therapy for nocturnal panic. *Behavior Therapy*, 36, 43–54.
- Craske, M.G., Roy-Byrne, P., Stein, M.B. *et al.* (2006) CBT intensity and outcome for panic disorder in a primary care setting. *Behavior Therapy*, 37, 112–119.
- Craske, M.G., Farchione, T., Allen, L. *et al.* (2007) Cognitive behavioral therapy for panic disorder and comorbidity: more of the same or less of more. *Behaviour Research and Therapy*, 45, 1095–1109.
- Craske, M.G., Kircanski, K., Zelikowsky, M. *et al.* (2008) Optimizing inhibitory learning during exposure therapy. *Behaviour Research and Therapy*, 46, 5–27.

- Craske, M.G., Kircanski, K., Epstein, A. *et al.* (2010) Panic disorder: a review of DSM-IV panic disorder and proposals for DSM-V. *Depression and Anxiety*, 27, 93–112.
- Craske, M.G., Stein, M.B., Sullivan, G. *et al.* (2011) Disorder-specific impact of coordinated anxiety learning and management treatment for anxiety disorders in primary care. *Archives of General Psychiatry*, 68, 378–388.
- Craske, M.G., Liao, B., Brown, L., and Vervliet, B. (2012) Role of inhibition in exposure therapy. *Journal of Experimental Psychopathology*, 3, 322–345.
- Culver, N.C., Stoyanova, M., and Craske, M.G. (2011) Clinical relevance of retrieval cues for attenuating context renewal of fear. *Journal of Anxiety Disorders*, 25, 284–292.
- Debiec, J. and Le Doux, J.E. (2004) Disruption of reconsolidation but not consolidation of auditory fear conditioning by noradrenergic blockade in the amygdala. *Neuroscience*, 129, 267–272.
- Dow, M., Kenardy, J., Johnston, D. *et al.* (2007) Prognostic indices with brief and standard CBT for panic disorder: I. predictors of outcome. *Psychological Medicine*, 27, 1493–1502.
- Dworkin, B.R. and Dworkin, S. (1999) Heterotopic and homotopic classical conditioning of the baroreflex. *Integrative Physiological and Behavioral Science*, 34, 158–176.
- Ehlers, A. (1995) A 1-year prospective study of panic attacks: clinical course and factors associated with maintenance. *Journal of Abnormal Psychology*, 104, 164–172.
- Ehlers, A. and Margraf, J. (1989) The psychophysiological model of panic attacks, in *Anxiety Disorders: Annual Series of European Research in Behavior Therapy*, vol. 4 (ed. P.M.G. Emmelkamp), Swets, Amsterdam.
- Ehlers, A., Margraf, J., Roth, W.T. *et al.* (1988) Anxiety induced by false heart rate feedback in clients with panic disorder. *Behaviour Research and Therapy*, 26 (1), 1–11.
- Eley, T. (2001) Contributions of behavioral genetics research: quantifying genetic, shared environmental and nonshared environmental influences, in *The Developmental Psychopathology of Anxiety* (eds M. Vasey and M. Dadds), Oxford University Press, New York, pp. 45–59.
- Eysenck, H.J. (1967) *The Biological Basis of Personality*, C.C. Thomas, Springfield, IL.
- Fava, G.A., Porcelli, P., Faranelli, C. *et al.* (2010) The spectrum of anxiety disorders in the medically ill. *Journal of Clinical Psychiatry*, 71, 910–914.
- Feigenbaum, W. (1988) Long-term efficacy of ungraded versus graded massed exposure in agoraphobics, in *Panic and Phobias: Treatments and Variables Affecting Course and Outcome* (eds I. Hand and H. Wittchen), Springer, Berlin.
- Foa, E.B. and Kozak, M.J. (1986) Emotional processing of fear: exposure to corrective information. *Psychological Bulletin*, 99, 20–35.
- Foa, E.B. and McNally, R.J. (1996) Mechanisms of change in exposure therapy, in *Current Controversies In the Anxiety disorders* (ed. R.M. Rapee), Guilford Press, New York, pp. 229–343.
- Garssen, B., de Ruiter, C., and van Dyck, R. (1992) Breathing retraining: a rational placebo? *Clinical Psychology Review*, 12, 141–153.
- Gloster, A.T., Wittchen, H.U., Einsle, F. *et al.* (2011) Psychological treatment for panic disorder with agoraphobia: a randomized controlled trial to examine the role of therapist-guided exposure in situ in CBT. *Journal of Consulting and Clinical Psychology*, 79, 406–420.
- Goodwin, R., Fergusson, D., and Horwood, L. (2005) Childhood abuse and familial violence and the risk of panic attacks and panic disorder in young adulthood. *Psychological Medicine*, 35, 881–890.
- Gorman, J.M., Papp, L.A., Coplan, J.D. *et al.* (1994) Anxiogenic effects of CO₂ and hyperventilation in clients with panic disorder. *American Journal of Psychiatry*, 151 (4), 547–553.
- Gray, J.A. (1982) *The Neuropsychology of Anxiety: An Enquiry into the Functions of the Septo-hippocampal System*, Oxford University Press, New York.

- Haby, M., Donnelly, M., Corry, J., and Vos, T. (2006) Cognitive behavioural therapy for depression, panic disorder and generalized anxiety disorder: a meta-regression of factors that may predict outcome. *Australian and New Zealand Journal of Psychiatry*, 40, 9–19.
- Hays, P. and Iwamasa, G. (2006) *Culturally Responsive Cognitive Behavioral Therapy: Assessment, Practice, and Supervision*, American Psychological Association, Washington, DC.
- Hayward, C., Killen, J.D., Kraemer, H.C., and Taylor, C.B. (2000) Predictors of panic attacks in adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry*, 39, 207–214.
- Hoffart, A. and Hedley, L.M. (1997) Personality traits among panic disorder with agoraphobia clients before and after symptom-focused treatment. *Journal of Anxiety Disorders*, 11, 77–87.
- Hofmann, S.G. (2006) The importance of culture in cognitive and behavioral practice. *Cognitive and Behavioral Practice*, 13, 243–245.
- Hope, D.A., Rapee, R.M., Heimberg, R.G., and Dombek, M.J. (1990) Representations of the self in social phobia: vulnerability to social threat. *Cognitive Therapy and Research*, 14, 177–189.
- van den Hout, M., Brouwers, C., and Oomen, J. (2006) Clinically diagnosed axis II comorbidity and the short term outcome of CBT for axis I disorders. *Clinical Psychology and Psychotherapy*, 13 (1), 56–63.
- Hwang, W. (2006) The psychotherapy adaptation and modification framework: application to Asian Americans. *American Psychologist*, 61, 702–715.
- Hwang, W. and Wood, J.J. (2007) Being culturally sensitive is not the same as being culturally competent. *Pragmatic Case Studies in Psychotherapy*, 3, 44–50.
- Katschnig, H. and Amering, M. (1998) The long-term course of panic disorder and its predictors. *Journal of Clinical Psychopharmacology*, 18 (6, Suppl 2), 6S–11S.
- Kendler, K.S., Heath, A.C., Martin, N.G., and Eaves, L.J. (1987) Symptoms of anxiety and symptoms of depression: same genes, different environments? *Archives of General Psychiatry*, 44, 451–457.
- Kessler, R.C., Berglund, P., Demler, O. *et al.* (2005a) Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*, 62, 593–602.
- Kessler, R.C., Chiu, W.T., Demler, O. *et al.* (2005b) Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*, 62, 617–627.
- Kindt, M., Soeter, M., and Vervliet, B. (2009) Beyond extinction: erasing human fear responses and preventing the return of fear. *Nature Neuroscience*, 12, 256–258.
- Kircanski, K., Mortazavi, A., Castriotta, N. *et al.* (2012) Challenges to the traditional fear hierarchy in exposure therapy. *Journal of Behavior Therapy and Experimental Psychiatry*, 43, 745–751.
- Kroeze, S. and van den Hout, M.A. (2000) Selective attention for cardiac information in panic clients. *Behaviour Research and Therapy*, 38, 63–72.
- Laberge, B., Gauthier, J.G., Cote, G. *et al.* (1993) Cognitive-behavioral therapy of panic disorder with secondary major depression: a preliminary investigation. *Journal of Consulting and Clinical Psychology*, 61, 1028–1037.
- Lake, R.I.E., Eaves, L.J., Maes, H.H.M. *et al.* (2000) Further evidence against the environmental transmission of individual differences in neuroticism from a collaborative study of 45,850 twins and relatives of two continents. *Behavior Genetics*, 30 (3), 223–233.
- Lang, A.J. and Craske, M.G. (2000) Manipulations of exposure-based therapy to reduce return of fear: a replication. *Behaviour Research and Therapy*, 38, 1–12.

- Latas, M., Starcevic, V., Trajkovic, G., and Bogojevic, G. (2000) Predictors of comorbid personality disorders in clients with panic disorder with agoraphobia. *Comprehensive Psychiatry*, 41, 28–34.
- Lehman, C.L., Brown, T.A., and Barlow, D.H. (1998) Effects of cognitive-behavioral treatment for panic disorder with agoraphobia on concurrent alcohol abuse. *Behavior Therapy*, 29, 423–433.
- Lehrer, P., Karavidas, M., Lu, S. *et al.* (2008) Psychological treatment of comorbid asthma and panic disorder: a pilot study. *Journal of Anxiety Disorders*, 22, 671–683.
- Lewis-Fernandez, R., Hinton, D.E., Laria, A.J. *et al.* (2010) Culture and the anxiety disorders: recommendations for DSM-V. *Depression and Anxiety*, 27, 212–229.
- Lovibond, P.F., Davis, N.R., and O’Flaherty, A.S. (2000) Protection from extinction in human fear conditioning. *Behaviour Research and Therapy*, 38, 967–983.
- Maidenberg, E., Chen, E., Craske, M. *et al.* (1996) Specificity of attentional bias in panic disorder and social phobia. *Journal of Anxiety Disorders*, 10, 529–541.
- Maier, S.F., Laudenslager, M.L., and Ryan, S.M. (1985) Stressor controllability, immune function and endogenous opiates, in *Affect, Conditioning and Cognition: Essays on the Determinants of Behavior* (eds F.R. Brush and J.B. Overmeier), Lawrence Erlbaum, Hillsdale, NJ, pp. 183–201.
- Maller, R.G. and Reiss, S. (1992) Anxiety sensitivity in 1984 and panic attacks in 1987. *Journal of Anxiety Disorders*, 6, 241–247.
- Marchand, A., Goyer, L.R., Dupuis, G., and Mainguy, N. (1998) Personality disorders and the outcome of cognitive-behavioural treatment of panic disorder with agoraphobia. *Canadian Journal of Behavioural Science*, 30 (1), 14–23.
- Marchesi, C., Cantoni, A., Fonto, S. *et al.* (2005) The effect of pharmacotherapy on personality disorders in panic disorder: a one year naturalistic study. *Journal of Affective Disorders*, 89, 189–194.
- Marks, I., Basoglu, M., Noshirvani, H. *et al.* (1993) Drug treatment of panic disorder: further comment. *British Journal of Psychiatry*, 162, 795–796.
- Marshall, J.R. (1997) Alcohol and substance abuse in panic disorder. *Journal of Clinical Psychiatry*, 58, 46–49.
- Martin, N.G., Jardine, R., Andrews, G., and Heath, A.C. (1988) Anxiety disorders and neuroticism: are there genetic factors specific to panic? *Acta Psychiatrica Scandinavica*, 77, 698–706.
- McNally, R.J. and Lorenz, M. (1987) Anxiety sensitivity in agoraphobics. *Journal of Behavior Therapy and Experimental Psychiatry*, 18 (1), 3–11.
- Meuret, A.E., Wilhelm, F., Ritz, T., and Roth, W. (2008) Feedback of end-tidal pCO₂ as a therapeutic approach for panic disorder. *Journal of Psychiatric Research*, 42, 560–568.
- Meuret, A.E., Rosenfield, D., Seidel, A. *et al.* (2010) Respiratory and cognitive mediators of treatment change in panic disorder: evidence for intervention specificity. *Journal of Consulting and Clinical Psychology*, 78, 691–704.
- Meuret, A.E., Wolitzky-Taylor, K.B., Twohig, M.P., and Craske, M.G. (2012) Coping skills and exposure therapy in panic disorder and agoraphobia: Latest advances and future directions. *Behavior Therapy*, 43, 271–284.
- Miranda, J., Bernal, G., Lau, A. *et al.* (2005) State of the science on psychosocial interventions for ethnic minorities. *Annual Review of Clinical Psychology*, 1, 113–142.
- Mystkowski, J.L., Craske, M.G., Echiverri, A.M., and Labus, J.S. (2006) Mental reinstatement of context and return of fear in spider-fearful participants. *Behavior Therapy*, 37 (1), 49–60.
- Nader, K., Schafe, G.E., and Le Doux, J.E. (2000) Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. *Nature*, 406, 722–726.

- Neumann, D.L., Lipp, O.V., and Cory, S.E. (2007) Conducting extinction in multiple contexts does not necessarily attenuate the renewal of shock expectancy in a fear-conditioning procedure with humans. *Behaviour Research and Therapy*, 45, 385–394.
- Norberg, M.M., Krystal, J.H., and Tolin, D.F. (2008) A meta-analysis of d-cycloserine and the facilitation of fear extinction and exposure therapy. *Biological Psychiatry*, 63, 1118–1126.
- Norton, P. and Price, E. (2007) A meta-analytic review of adult cognitive-behavioral treatment outcome across the anxiety disorders. *Journal of Nervous and Mental Disease*, 195, 521–531.
- Noyes, R., Crowe, R.R., Harris, E.L. *et al.* (1986) Relationship between panic disorder and agoraphobia: a family study. *Archives of General Psychiatry*, 43, 227–232.
- Otto, M.W., Tolin, D.F., Simon, N.M. *et al.* (2010) Efficacy of d-cycloserine for enhancing response to cognitive-behavior therapy for panic disorder. *Biological Psychiatry*, 67, 365–370.
- Ozkan, M. and Altindag, A. (2005) Comorbid personality disorders in subjects with panic disorder: do personality disorders increase clinical severity? *Comprehensive Psychiatry*, 46, 20–26.
- Pauli, P., Amrhein, C., Muhlberger, A. *et al.* (2005) Electroocutaneous evidence for an early abnormal processing of panic-related words in panic disorder clients. *International Journal of Psychophysiology*, 57, 33–41.
- Perna, G., Bertani, A., Arancio, C. *et al.* (1995) Laboratory response of clients with panic and obsessive-compulsive disorders to 35% CO₂ challenges. *American Journal of Psychiatry*, 152, 85–89.
- Rachman, S., Shafran, R., Radomsky, A.S., and Zysk, E. (2011) Reducing contamination by exposure plus safety behaviour. *Journal of Behavior Therapy and Experimental Psychiatry*, 42, 397–404.
- Rapee, R.M., Brown, T.A., Antony, M.M., and Barlow, D.H. (1992) Response to hyperventilation and inhalation of 5.5% carbon dioxide-enriched air across the DSM-III-R anxiety disorders. *Journal of Abnormal Psychology*, 101, 538–552.
- Razran, G. (1961) The observable unconscious and the inferable conscious in current Soviet psychophysiology: interoceptive conditioning, semantic conditioning, and the orienting reflex. *Psychological Review*, 68, 81–147.
- Reiss, S. (1980) Pavlovian conditioning and human fear: An expectancy model. *Behavior Therapy*, 11, 380–396.
- Rief, W., Trenkamp, S., Auer, C., and Fichter, M.M. (2000) Cognitive behavior therapy in panic disorder and comorbid major depression. A naturalistic study. *Psychotherapy and Psychosomatics*, 69, 70–78.
- Rescorla, R.A. (2006) Deepened extinction from compound stimulus presentation. *Journal of Experimental Psychology: Animal Behavior Processes*, 32, 135–144.
- Rowe, M.K. and Craske, M.G. (1998) Effects of an expanding-spaced vs massed exposure schedule on fear reduction and return of fear. *Behaviour Research and Therapy*, 36, 701–717.
- Roy-Byrne, P.P. and Cowley, D.S. (1995) Course and outcome in panic disorder: A review of recent follow-up studies. *Anxiety*, 1, 151–160.
- Roy-Byrne, P., Craske, M.G., Stein, M.B. *et al.* (2005) A randomized effectiveness trial of cognitive-behavioral therapy and medication for primary care panic disorder. *Archives of General Psychiatry*, 62, 290–298.
- Salkovskis, P.M. (1991) The importance of behaviour in the maintenance of anxiety and panic: A cognitive account. *Behavioural Psychotherapy*, 19 (1), 6–19.

- Salkovskis, P.M., Clark, D.M., and Gelder, M.G. (1996) Cognition-behaviour links in the persistence of panic. *Behaviour Research and Therapy*, 34, 453–458.
- Schmidt, N.B., Lerew, D.R., and Jackson, R.J. (1997) The role of anxiety sensitivity in the pathogenesis of panic: prospective evaluation of spontaneous panic attacks during acute stress. *Journal of Abnormal Psychology*, 106, 355–364.
- Schmidt, N.B., Lerew, D.R., and Jackson, R.J. (1999) Prospective evaluation of anxiety sensitivity in the pathogenesis of panic: replication and extension. *Journal of Abnormal Psychology*, 108, 532–537.
- Simos, G. (2002) Cognitive behavior therapy for panic disorder, in *Cognitive Behavior Therapy: A Guide for Practicing Clinicians*, vol 1. (ed. G. Simos), Brunner-Routledge, Hove.
- Sloan, T. and Telch, M.J. (2002) The effects of safety-seeking behavior and guided threat reappraisal on fear reduction during exposure: An experimental investigation. *Behaviour Research and Therapy*, 40 (3), 235–251.
- Soeter, M. and Kindt, M. (2010) Dissociating response systems: erasing fear from memory. *Neurobiology of Learning and Memory*, 94, 30–41.
- Sokolowska, M., Siegel, S., and Kim, J.A. (2002) Intraadministration associations: Conditional hyperalgesia elicited by morphine onset cues. *Journal of Experimental Psychology: Animal Behavior Processes*, 28 (3), 309–320.
- Sotres-Bayon, F., Cain, C.K., and LeDoux, J.E. (2006) Brain mechanisms of fear extinction: historical perspectives on the contribution of prefrontal cortex. *Biological Psychiatry*, 60, 329–336.
- Spiegel, D.A., Bruce, T.J., Gregg, S.F., and Nuzzarello, A. (1994) Does cognitive behavior therapy assist slow-taper alprazolam discontinuation in panic disorder? *American Journal of Psychiatry*, 151 (6), 876–881.
- Telch, M.J., Lucas, J.A., and Nelson, P. (1989) Nonclinical panic in college students: an investigation of prevalence and symptomatology. *Journal of Abnormal Psychology*, 98, 300–306.
- Tsao, J.C.I., Lewin, M.R., and Craske, M.G. (1998) The effects of cognitive-behavior therapy for panic disorder on comorbid conditions. *Journal of Anxiety Disorders*, 12, 357–371.
- Tsao, J.C.I., Mystkowski, J.L., Zucker, B.G., and Craske, M.G. (2005) Impact of cognitive-behavioral therapy for panic disorder on comorbidity: A controlled investigation. *Behaviour Research and Therapy*, 43, 959–970.
- Vansteenwegen, D., Vervliet, B., Iberico, C. *et al.* (2007) The reported confrontation with videotapes of spiders in multiple contexts attenuates renewal of fear in spider-anxious students. *Behaviour Research and Therapy*, 45, 1169–1179.
- Veltman, D.J., van Zijderveld, G., Tilders, F.J.H., and van Dyck, R. (1996) Epinephrine and fear of bodily sensations in panic disorder and social phobia. *Journal of Psychopharmacology*, 10 (4), 259–265.
- Walker, D.L., Ressler, K.J., Lu, K.T., and Davis, M. (2002) Facilitation of conditioned fear extinction by systemic administration or intraamygdala infusions of D-cycloserine as assessed with fear potentiated startle in rats. *Journal of Neuroscience*, 22, 2345–2351.
- Wardle, J., Hayward, P., Higgitt, A. *et al.* (1994) Effects of concurrent diazepam treatment on the outcome of exposure therapy in agoraphobia. *Behaviour Research and Therapy*, 32, 203–215.
- Watson, D. and Clark, L.A. (1984) Negative affectivity: The disposition to experience aversive emotional states. *Psychological Bulletin*, 96 (3), 465–490.
- Weems, C.F., Hayward, C., Killen, J., and Taylor, C.B. (2002) A longitudinal investigation of anxiety sensitivity in adolescence. *Journal of Abnormal Psychology*, 111 (3), 471–477.

- Westra, H.A., Stewart, S.H., and Conrad, B.E. (2002) Naturalistic manner of benzodiazepine use and cognitive behavioral therapy outcome in panic disorder and agoraphobia. *Journal of Anxiety Disorders*, 16 (3), 223–246.
- Wittchen, H.U., Gloster, A.T., Beesdo-Baum, K. *et al.* (2010) Agoraphobia: a review of the diagnostic classificatory position and criteria. *Depression and Anxiety*, 27, 113–133.
- Wolitzky-Taylor, K.B., Castriotta, N., Lenze, E.J. *et al.* (2010) Anxiety disorders in older adults: a comprehensive review. *Depression and Anxiety*, 27, 190–211.
- Wolpe, J. (1959) *Psychotherapy Based on the Principle of Reciprocal Inhibition*, Prentice-Hall, Oxford.
- Zinbarg, R.E., Barlow, D.H., and Brown, T.A. (1997) Hierarchical structure and general factor saturation of the anxiety sensitivity index: Evidence and implication. *Psychological Assessment*, 9, 277–284.