

Cognitive-Behavioral Therapy and the Treatment of Panic Disorder: Efficacy and Strategies

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In this article, we review the efficacy and applications of cognitive-behavioral therapy (CBT) for panic disorder. Research supports CBT as an effective first-line treatment of panic disorder that offers relatively quick onset of action and long-term maintenance of treatment benefits. These characteristics, plus the acceptability, tolerability, and cost-efficacy of CBT, make it an especially attractive treatment option for panic disorder. We review these findings as well as some newer developments in the field including research on emotional acceptance, the importance of context in extinction learning, and the use of CBT in combination with pharmacotherapy.

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Research on the application of cognitive-behavioral therapy (CBT) to the treatment of panic disorder is particularly well developed. Advancing from initial wait-list and placebo-controlled comparison trials¹ to complex combined-treatment trials,² CBT for panic disorder has also undergone evaluations of the necessary elements of treatment,³ transportability of treatment to nonresearch settings,⁴ cost-efficacy issues,⁵ and the application of CBT to the prevention of panic disorder onset.⁶

In this article, we review studies of the acceptability and efficacy of CBT for panic disorder and discuss some recent conceptualizations of the nature of the changes in emotional processing that can result from CBT. In addition, we devote attention to factors that may influence the efficacy of CBT, including research on emotional acceptance, safety behaviors, and the ways in which combination treatment strategies—CBT plus pharmacotherapy—may interact to help or hinder treatment outcome.

ELEMENTS OF TREATMENT

Cognitive-behavioral therapies for anxiety disorders share the common goal of helping patients relearn a sense of safety in relation to feared cues.⁷ For panic disorder, the feared cues are anxiety sensations themselves, and these

fears are thought to predispose patients to initial panic attacks, maintain the disorder once developed, and predict relapse among partially treated patients.^{8,9} Treatment is initiated with informational discussions designed to provide patients with an understanding of the cascade of anxiety and panic symptoms, role of thoughts, conditioned fears of symptoms, and avoidance in the maintenance of panic disorder. Informational interventions also provide the rationale for the CBT interventions to follow. Informational interventions delivered at the start of treatment are followed by rehearsal of concepts and procedures in the session, with subsequent assignment of rehearsals of these procedures outside the clinic, in the moments of patients' lives when these procedures are most applicable. Helping a patient quickly gain perspective on the nature of his or her disorder and the interventions to be applied is particularly important given the brevity of CBT for panic disorder—often in the range of 12 to 15 weekly sessions.

The systematic relearning of safety in the presence of internal (anxiety sensations) or external (phobic situations) fear cues occurs through 2 main treatment components: exposure and cognitive restructuring.¹⁰ Exposure is directed to both the feared bodily sensations thought to be at the root of panic disorder (interoceptive exposure) and the external situations in which these fears arise (in vivo exposure). Interoceptive exposure involves exposing oneself to feared bodily sensations (e.g., using hyperventilation to induce dizziness, hot flushes, and tingling, or shaking the head from side to side to induce feelings of dizziness or derealization). In vivo exposure involves exposure to situations that patients fear and avoid such as public transportation, crowds, and lines.

Cognitive restructuring interventions are used to help patients modify automatic thoughts and assumptions about the dangerousness of the sensations and situations.

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By testing the accuracy of their self-talk and assumptions (e.g., “I will faint,” “I can’t stand these feelings”), patients learn that their worst fears are not inevitable outcomes. Cognitive restructuring has direct effects on reducing fears of interoceptive and external cues, and it also aids patients in feeling confident enough to engage in the exposure procedures that help lock in fear reduction.

EFFICACY, TOLERABILITY, AND EFFECTIVENESS OF TREATMENT

A wealth of individual studies, summarized in meta-analytic comparisons,¹¹ have indicated that CBT is an efficacious treatment for patients with panic disorder, with strong maintenance of treatment gains over time. Cognitive-behavioral therapy for panic disorder also offers relatively fast onset of action¹² and benefits to patients who have failed to respond to adequate trials of pharmacotherapy.¹³ Research from controlled clinical trials also indicates that CBT is accepted and well tolerated by patients.^{11,14,15} For example, a recent multicenter study of panic disorder noted that less than 1% of individuals who refused randomization did so because they were concerned about CBT.¹⁴ This was in contrast to the 34% who refused to participate because of concern over treatment with imipramine.¹⁴ Similarly, dropout rates from controlled clinical trials (an index of the tolerability of treatment) indicate that CBT for panic disorder is at least as tolerable as pharmacologic alternatives.^{11,15}

Comorbidity is common in panic disorder, and research suggests that patients with panic disorder with and without comorbid depression show similar response to CBT.^{16,17} There is also evidence that CBT for panic disorder can positively impact comorbid conditions, although this is not always the case.¹⁸ For example, Tsao and colleagues¹⁷ found that depression, generalized anxiety disorder, and specific phobia improved after a 16-session CBT treatment for panic disorder. Rates of comorbid diagnoses decreased from 60.8% prior to treatment to 37.3% after treatment, and these improvements were maintained at a 6-month follow-up evaluation.

There is also evidence that CBT can be successfully exported from research settings to community clinics and is particularly cost-effective. Specifically, a 15-session, manualized CBT protocol for panic disorder can be effectively administered in a community mental health center and has short- and long-term treatment gains that are equivalent to those in clinical trials.^{4,19} In terms of the costs of treatment, Otto et al.⁵ determined that group CBT was the most cost-effective treatment for individuals with panic disorder during the acute phase (\$518), with even clearer cost advantages at 1 year (\$523). Individual CBT was more expensive than were pharmacologic treatments during the acute phase (\$1357 vs. \$839, respectively); however, it proved to be more cost-effective over a 1-year

period, being 59% of the cost of pharmacologic treatments over the same interval.

Support for a cognitive-behavioral model of panic disorder and its treatment also extends to prevention studies. Specifically, Gardenswartz and Craske⁶ identified individuals at risk for panic disorder (high fears of anxiety sensations, experiencing occasional panic attacks) and randomly assigned them to either a wait-list condition or a 5-hour panic disorder prevention workshop consisting of education about panic disorder, interoceptive exposure, and cognitive restructuring. Preventive effects were evident at the 6-month assessment; 13.6% of individuals in the control condition had emergent panic disorder compared to 1.8% of individuals receiving the preventive treatment. Taken together, this literature suggests that CBT for panic disorder is a durable treatment of equivalent efficacy to pharmacologic interventions, but with potential advantages in terms of patient acceptability, cost, and maintenance of treatment gains.

EMOTIONAL REGULATION AND FURTHER APPLICATIONS OF CBT FOR PANIC DISORDER

Recent accounts of the efficacy of CBT for the anxiety disorders have emphasized the systematic relearning of safety in response to phobic cues, with particular emphasis on altering responses to emotional arousal. Consistent with this approach, Barlow and colleagues²⁰ have emphasized reductions in emotional avoidance as well as the facilitation of adaptive behaviors in response to emotions as core strategies relevant to a range of emotional disorders. Furthermore, the emphasis on training alternative responses to emotional content is consistent with the promotion of emotional acceptance/tolerance in a variety of disorders that is increasingly being discussed by cognitive-behavioral researchers.^{21–23}

Although many of these strategies include training in mindfulness, exposure-based procedures also involve training in emotional acceptance. For example, interoceptive exposure is designed to help patients respond to anxiety sensations by noting the sensations and doing nothing to try to control them. These experiences help patients learn that they can be “OK” despite the presence of anxiety, and help stop the escalation of initial anxiety sensations into panic attacks. In addition to learning not to fear somatic sensations of anxiety, patients also learn to select useful (nonavoidance) behaviors under “hot” emotional conditions.²⁴

This approach has also been used to help patients with panic disorder taper from antianxiety medications, such as benzodiazepines, and withstand the withdrawal and anxiety sensations that accompany this process. Although this treatment incorporated traditional CBT elements such as information, cognitive restructuring, and interoceptive exposure, particular attention was given to the training of

alternate responses to benzodiazepine use in the face of fears of anxiety and withdrawal sensations. Thus far, this approach has met with promising results.²⁵

It is interesting to note that the training of adaptive responses to emotional cues is also at the heart of novel approaches to drug abuse treatment²⁶ and indicates the potentially diverse application of this approach. In this treatment, emotions that typically cue drug use behavior are induced in session (similar to interoceptive exposure but using emotional cues other than anxiety sensations), and both acceptance strategies and more adaptive behaviors (than drug use) are rehearsed in response to these emotions.²⁴

Attention to the learning of acceptance/adaptive responses to emotional cues is consistent with modifications of CBT for panic disorder, specifically the elimination of strategies that focus on controlling affect. For example, relaxation training and benzodiazepine use have been shown to decrease panic symptoms and benefit patients with panic disorder,³ but research suggests that treatments that incorporate these elements are less efficacious than exposure-based procedures.¹¹ In fact, muscle relaxation training and diaphragmatic breathing retraining offer no additive benefits (and may reduce longer-term efficacy) for patients with panic disorder compared to treatment packages offering information, exposure, and cognitive restructuring alone.³ One interpretation of these findings is that relaxation procedures may inadvertently encourage continued escape, distraction, or avoidance of anxiety sensations, allowing core fears of these sensations to remain untreated.²⁵

SAFETY BEHAVIORS AND CONTEXT-SPECIFIC LEARNING

There is a growing body of evidence suggesting that the use of safety behaviors—avoidance, distraction, or rescue procedures designed to avert or attenuate anxiety in phobic situations—may reduce anxiety in the moment but also reduce the efficacy of exposure over time.^{27,28} For example, Powers et al.²⁹ investigated the degree to which safety behaviors interfered with the benefits of exposure-based CBT in adults with syndromal (75%) or subsyndromal (25%) claustrophobia. Individuals who received encouragement of safety behaviors during exposure, as well as those who had safety behaviors available but were not given the same encouragement to use them, achieved less benefit from the treatment than participants treated with exposure alone: 94% of exposure-alone patients achieved high end-state functioning at posttreatment, compared to 45% for the 2 safety behavior conditions, and 25% and 0% for the placebo and wait-list conditions, respectively.

One clear implication of these findings is that clinicians and anxiety patients should carefully consider the use of

safety behaviors, i.e., carrying “rescue” medications such as benzodiazepines in phobic situations. Carrying these medications may attenuate fears during any given exposure, but this practice may slow improvement over time. This principle is consistent with the notion that what is learned in exposure in one context (i.e., when safety behaviors or medications are available) may not extend to a subsequent context (no safety behaviors or medications available). These exact considerations have been the topic of a wealth of animal research.

Numerous animal studies suggest that relearning of safety in response to feared cues (extinction) is often dependent on the particular context of that learning.³⁰ For example, animals conditioned to fear a stimulus in context A, who undergo fear extinction in context B, demonstrate a return of fear when again exposed to the stimulus in context A. In other words, even though fearful responses to the stimulus appear to be eliminated in the exposure (extinction) context, if the context is changed, fear behaviors may reemerge. Moreover, extinction is sensitive to context shifts such as changing the room of testing or training, other environmental and external background stimuli, recent events, and the passage of time.³⁰

Such situational context effects have been demonstrated in clinical studies of humans. For example, Rodriguez et al.³¹ showed that in patients with fear of spiders, the degree of fear reduction from exposure was attenuated when participants were tested in a different context from the setting in which the exposure was conducted. Studies like this underscore the clinical principle that for skills learned in session to be fully valuable for a patient, they must be practiced independently of the therapist, in the moments in the patient’s life when the skills are most relevant. In other words, clinicians providing CBT must routinely ensure that fear reduction occurs in multiple contexts, particularly contexts that do not include the therapist or safety behaviors used by the patient.

CONTEXT EFFECTS AND COMBINATION TREATMENT

The importance of ensuring that exposure procedures are rehearsed in a variety of contexts also extends to shifts in internal context. Specifically, Bouton and colleagues³² administered benzodiazepine or saline in order to change the internal context of animals undergoing fear extinction. Just as shifts in external contexts can influence extinction, the study showed that animals undergoing a shift in internal context between extinction and later testing have poorer maintenance of extinction effects. Similar findings have been documented in human adults undergoing treatment for fear of spiders. Mystkowski et al.³³ manipulated internal context with the ingestion of either caffeine (C) or placebo (P) prior to exposure procedures. Fear reduction was subsequently evaluated under test conditions that

were either congruent (i.e., C extinction and C testing or P extinction and P testing) or incongruent (C extinction and P testing or the reverse) with the exposure context. Exposure treatment was effective, and no difference between conditions was evident immediately at posttreatment. However, follow-up testing 1 week later revealed that patients tested under the incongruent condition had a greater return of fear than those in a congruent condition.

Based on these findings, Otto and associates³⁴ have argued that the changed internal context provided by medication underlies evidence of poorer maintenance of treatment gains in individuals who received combination treatment (short-term CBT combined with pharmacotherapy) relative to those who received CBT alone.² The poorer outcome emerges at the point of context shift, when patients in the combined treatment condition discontinue their pharmacotherapy. At this point in time, there is loss of efficacy for patients in the combined treatment condition relative to those who were medication free—suggesting that the benefits of CBT learned in the context of medication are not necessarily maintained when medication is discontinued. This shift in context appears to be due to internal cues (the feeling of being on the medication) because a shift in pill taking alone (discontinuing placebo medication) did not appear to hasten relapse.²

What are the implications of these findings for combination treatment strategies? Are these strategies doomed to poorer outcome than CBT alone (assuming existing findings are replicated)? Research suggests that combination treatments may have additive benefits for patients with panic disorder when the combination is employed during specific phases of treatment. For example, there is evidence that the combination of antidepressant treatment and CBT can be superior to either component alone while medication use is maintained.² However, given the ample evidence that inadequate treatment and medication discontinuation appear to be the rule rather than the exception in clinical practice,³⁵ and since there is evidence for the loss of long-term efficacy relative to patients treated with CBT alone even when medications are maintained for 6 months,² the use of combined treatments for panic disorder should be approached cautiously.

Fortunately, should patients and clinicians elect to pursue combination treatment, there is evidence that CBT can be reapplied at the point of medication discontinuation to allow patients to discontinue their medication successfully while extending their treatment gains.³⁵ Relative to context effects, the reapplication of CBT during and after medication discontinuation helps provide adaptive learning of CBT across the context change brought by medication discontinuation. The success of this approach is supported by medication discontinuation studies that examined the application of CBT to help patients with panic disorder maintain or extend their treatment gains while discontinuing benzodiazepine²⁵ or antidepressant treatment.³⁶

In summary, CBT for the anxiety disorders involves the systematic relearning of safety in response to both internal and external phobic cues. This learning is aided by informational, exposure, and cognitive-restructuring interventions; to achieve treatment effects that last, learning should cut across multiple contexts and be independent of the application of safety behaviors. Medication use appears to be a powerful context; what is learned during treatment with medication may not extend to a medication discontinuation period. Accordingly, patients who initially received CBT in the context of pharmacotherapy may need to reinstate CBT to maintain treatment gains across the context shift brought by medication discontinuation.

NOVEL APPROACHES TO COMBINATION TREATMENT

Achieving longer-term benefits in short-term CBT relies on helping patients with panic disorder develop alternative patterns of emotional regulation in response to anxiety symptoms. The magnitude of these learning effects is striking when one considers that many patients have their disorder chronically (e.g., for an average of 10 years) and that treatment alters these patterns within 10 to 13 hours of time with the CBT therapist.⁵ Moreover, each weekly 50-minute session accounts for less than 1% of an average person's waking life; with the goal of having the 1% of session influence the other 99% of waking life in an individual with a chronic disorder, special attention has to be placed on generalizing behaviors in the clinic to the home setting.³⁷ As noted earlier, CBT utilizes informational, exposure, and cognitive interventions, with attention to rehearsal of skills in multiple contexts to try to effect meaningful and long-lasting change. We have discussed how combined treatment, despite having the potential to boost treatment response when medication is maintained, may limit the staying power of CBT when medication is discontinued, but are there other pharmacologic approaches to boosting the effects of CBT that do not rely on anxiolysis and may be less susceptible to context or other interfering effects?

Advances in animal research suggest that the answer may be "yes." Specifically, the glutamatergic *N*-methyl-D-aspartate (NMDA) receptor has been shown to be critically involved in extinction learning, and this learning appears to be augmented by individual doses of NMDA agonists such as D-cycloserine.³⁸ Recent studies of adults with anxiety disorders suggest that the enhancement of learning during exposure exercises may lead to improved treatment outcome for individuals with anxiety disorders. In particular, Ressler et al.³⁹ randomly assigned 30 patients with a fear of heights (acrophobia) to virtual-reality exposure therapy in combination with single doses of D-cycloserine (50 mg or 500 mg) or placebo. Differential exposure effects were evident by the second session and

thereafter; patients who received D-cycloserine reported significantly less fear in response to height stimuli (perceived floors of elevation) than those treated with placebo. These benefits were maintained at a 3-month follow-up assessment, suggesting that the learning experienced during the exposure exercises may be maintained to a stronger degree when patients are taking the D-cycloserine.

These findings await replication and extension to other anxiety disorders. Nonetheless, they do introduce a new approach to combined treatment in which the pharmacotherapy is used to enhance memory rather than as an independent treatment for anxiety. This development may help enhance the already powerful effects of systematic exposure and may do so in a shorter amount of time than traditional CBT.

Drug name: imipramine (Tofranil and others).

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