Cognitive-Behavioral Therapy for Panic Disorder: Current Status

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Controlled clinical trials evaluating cognitive-behavioral approaches for panic disorder are rapidly accumulating. In the aggregate, these studies suggest substantial efficacy for cognitive-behavioral approaches in both the short and long term. Summaries and meta-analyses of these results are briefly described, but new evidence is also presented indicating that, in this chronic condition, patients continue to experience some exacerbations and remissions over the long term. Current attempts to evaluate combination psychosocial and pharmacologic approaches are described as well as the beginnings of efforts to develop more powerful treatments for panic disorder with or without agoraphobia.

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Early attempts to treat panic disorder with or without agoraphobia (PDA) using cognitive-behavioral procedures emphasized in vivo exposure strategies targeting agoraphobic avoidance.[1,2] The theoretical model for these approaches at that time suggested that phobic avoidance was associated with a classically conditioned fear response, and that it was necessary to facilitate habituation or extinction to the situations eliciting this response. When carried out properly, both avoidance behavior and the conditioned fear response would, presumably, be eliminated.

As with much early theorizing, these ideas proved overly simplistic. By the early 1980s, numerous studies had found that in vivo exposure-based procedures were consistently effective when compared to no treatment or some good psychosocial placebo, with 60% to 70% of these sometimes very severe cases showing substantial clinical benefit.[2,3] However, relatively few were "cured," and many patients continued to suffer from substantial anxiety and panic attacks despite improvement in their phobic behavior, thereby demonstrating a "desynchrony" between avoidance behavior and fear or anxiety.

During the early 1980s, and after the pioneering work of Donald Klein,[4,5] theoretical attention shifted to the nature and treatment of panic attacks within PDA. This led directly to a model of PDA that conceptualized the panic attack as a normal fear response that is misfiring under stressful life circumstances in individuals who are biologically and psychologically vulnerable to this "false alarm." While neither biological nor psychological vulnerabilities to PDA are fully understood, biological vulnerabilities are most often conceptualized as genetically influenced, labile, or overreactive autonomic nervous system and neuroendocrine responding, most likely associated with specific patterns of neurotransmitter activity. Psychological vulnerabilities, on the other hand, are typically characterized by cognitions that reflect extreme sensitivity to the possibility of physical injury or illness. Patients with psychological vulnerabilities are constantly vigilant for illness or injury, which is considered to be a very dangerous state of affairs. Vigilance for future danger is at the core of anxiety and reflects a basic sense of uncontrollability and unpredictability over future potentially dangerous life events. The psychological vulnerability to be anxious most likely develops during early rearing experiences in which children are not given a chance to develop coping styles and a sense of controllability or self-efficacy over life events that might prevent the later development of anxiety.[6] In addition, these individuals seem to come from a background where certain events, such as bodily illness or injury, are communicated to be a specific focus of danger.[2,7]

Thus, the model of PDA that guides cognitive-behavioral treatment suggests that panic attacks typically occur during very stressful life events and that people who ultimately develop panic disorder focus increasing amounts of anxiety on the possibility of having another attack, as well as on any bodily sensations that might signal the beginning of the next potentially dangerous panic attack. These benign bodily sensations may then become part of a vicious cycle in which the experience of sensations cues anxiety. Anxiety, in turn, increases the intensity of bodily sensations, which further increases anxiety until the patient eventually spirals into a high state of anxiety and,

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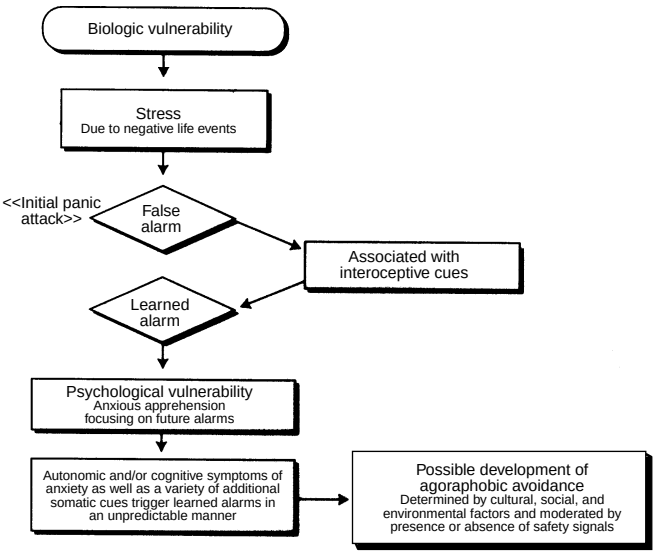
possibly, another panic attack. The initial panic attack, occurring in the context of life stress, would be considered a "false alarm" since this panic attack would represent the basic emotion of fear occurring at an inappropriate or unnecessary time. However, this false alarm would quickly become associated with internal bodily cues or interoceptive cues in the manner described above leading to increasingly frequent learned (conditioned) alarms. A number of people seem to experience this sequence of events without developing PDA. PDA seems to occur when the individual, in the context of a marked psychological vulnerability, focuses anxiety on the possibility of experiencing future panic attacks. A subset of these individuals, with a strong gender imbalance in which females are overrepresented, then go on to develop agoraphobic avoidance as one way of coping with the possibility of having unexpected and uncued panic attacks. This model of the development of panic disorder is presented in Figure 1.[2]

Figure 1. A Model of the Etiology of Panic Disorder*



*From reference 2, with permission.

Several specific versions of cognitive-behavioral therapy (CBT) for panic disorder have been developed. Perhaps the best known is referred to as panic control treatment.[8] Panic control treatment typically takes approximately 12 sessions, although additional sessions may be necessary depending on the extent and severity of agoraphobic avoidance. Most clinicians administer this program in a flexible manner interrupting it occasionally to deal with other clinical issues such as marital problems, etc. Approximately half the patients may show substantial benefit in 3 to 6 sessions. The remainder, particularly those with more severe agoraphobic avoidance, may need some additional attention beyond the usual 12-session length of the program. Panic control treatment consists of three major strategies: (1) cognitive restructuring, (2) breathing retraining, and (3) interoceptive or structured exposure to bodily sensations that have become associated with panic attacks.

COGNITIVE RESTRUCTURING

Cognitive restructuring was adapted from Beck's cognitive therapy for depression to be relevant for anxiety and panic. This phase of treatment focuses on correcting misappraisals of bodily sensations as dangerous events that may lead to death or loss of control. Carrying out cognitive therapy requires perhaps the most technical proficiency relative to other parts of treatment, since identifying core cognitions and pinpointing instances of overestimating the probability of dangerous events and/or "catastrophizing" about their consequences can be difficult.

BREATHING RETRAINING

Approximately 50% of those who have panic attacks experience symptoms associated with hyperventilation to some degree. The origins and physiologic basis of hyperventilation is carefully explained to the patient and is combined with a demonstration of the effects of hyperventilation in the office. Breathing retraining involves teaching proper diaphragmatic breathing until patients can breathe comfortably at the rate of 8 to 10 breaths per minute. Patients with panic disorder often find this difficult at first, but eventually master the technique so that they can use it during stressful periods in their day-to-day life.

INTEROCEPTIVE EXPOSURE

Since physical sensations most often trigger learned alarms in our model of panic disorder, the procedure of interoceptive exposure attempts to extinguish anxiety connected with these bodily sensations. Identifying "interoceptive avoidance," or avoidance of situations that might provoke specific physical sensations (in the mind of the patient), is also a task in therapy. These situations are not identical to agoraphobic situations and may include such activities as watching frightening movies, driving with the windows closed and the heater on, or even having sexual relations. All patients are presented with a standard series of exercises meant to induce physical sensations: running in place, being spun in a swivel chair, breathing through a narrow straw, etc. Patients are then encouraged to enter naturalistic situations that might be associated with the elicitation of physical sensations that are particularly anxiety-provoking (e.g., taking a sauna bath).

SITUATIONAL EXPOSURE

If agoraphobic avoidance complicates the disorder, a course of intensive in vivo exposure is administered until

Table 1. Clinical Trials of Cognitive-Behavioral Treatments for Panic Disorder Using an Intent-to-Treat Analysis*

Study	Length of Follow-Up, Months	Treatment/ Number of Patients/ % Panic Free	Significant Comparison (% Panic Free)[a]	
			Other Treatments	Wait List
Craske et al,[12] 1991[b]	24	PCT/15/81	Yes: AR = 36 Yes: PCT and AR = 43	…
Clark et al,[13] 1994	12	CT/17/76[c]	Yes: AR = 43[c] Yes: IMI = 48[c]	…
Klosko et al,[14] 1990	PT	PCT/15/87	No: AL = 50 Yes: PL = 36	Yes: 33
Newman et al,[15] 1990	12	CTM/24/87 CTNM/19/87	…	…
Côté et al,[16] 1992	12	CBTM/13/92 CBTM/8/100	…	…
Beck et al,[17] 1992	PT	CT/17/94	Yes: ST = 25[d]	…
Black et al,[18] 1993	PT	CT/25/32	Yes: FL = 68 No: PL = 20	…
Margraf and Schneider,[19] 1991	1	CT/22/91	…	Yes: 5
Öst et al,[20] 1993	12	CT/19/89[c]	No: AR = 74[c]	…
Telch et al,[21] 1993	PT	PCT/34/85	…	Yes: 30
Craske et al,[22] 1995	PT	CBT/16/53	Yes: NPT = 8	…
Shear et al,[23] 1994	6	CBT/23/45	No: NPT = 45	…

*Abbreviations: AL = alprazolam; AR = applied relaxation; CBT = cognitive-behavioral therapy; CBTM = cognitive-behavioral therapy and medication; CBTNM = cognitive-behavioral therapy without medication; CT = cognitive therapy; CTM = cognitive therapy and medication; CTNM = cognitive therapy without medication; FL = fluvoxamine maleate; IMI = imipramine hydrochloride; NPT = nonprescription treatment; PL = pill placebo; PCT = panic control treatment (exposure and cognitive restructuring); PT = posttreatment; ST = standard treatment.
[a]"Yes" = comparison was significant; "No" = comparison was not significant; "…" = no comparison made.
[b]Follow-up study of Barlow et al.[24]
[c]Percentage of patients who were panic free at follow-up and who had received no additional treatment during the follow-up period.
[d]At 8 weeks, which is the end of supportive therapy. At this time, 71% of patients undergoing cognitive therapy were panic free.

agoraphobic avoidance is substantially decreased or eliminated.[9]

SHORT- AND LONG-TERM CLINICAL TRIAL DATA ON THE EFFECTIVENESS OF CBT

Studies are rapidly accumulating that evaluate the efficacy and clinical utility of CBT for panic disorder. Gould et al.[10] recently compared the effectiveness of pharmacologic, cognitive-behavioral, and combined pharmacologic and cognitive-behavioral treatments in a meta-analysis of 43 controlled studies that included 76 treatment interventions. They reported that cognitive-behavioral treatments yielded the highest mean effect size (ES) (ES = 0.68). This compared favorably with pharmacologic treatments (ES = 0.47) as well as combination drug and CBT treatment (ES = 0.56). They also noted that the proportion of patients dropping out of CBT was 5.6% relative to higher percentages in treatments including the pharmacologic approaches. Particularly interesting was the fact that among cognitive-behavioral treatments, those studies that combined cognitive restructuring with interoceptive exposure, as is done in panic control treatment, yielded the strongest effect size (ES = 0.88). Long-term outcome analyses analyzed in the context of the main meta-analysis suggested that cognitive-behavioral interventions were successful at maintaining treatment gains.

Table 1[11] summarizes data from 12 studies specifically evaluating variants of cognitive-behavioral therapy for panic disorder utilizing an intent to treat analysis. In most studies, CBT was significantly more effective than alternative treatments, including alternative psychosocial treatments. Follow-ups ranging from 6 months to 24 months reveal that, for the most part, gains were maintained when patients were assessed cross-sectionally. Several of these studies are worth some comment since they represent exceptions to the generally positive results. For example, Craske et al.[22] attempted to reduce the length of panic control treatment from 12 sessions to 4 sessions and noted that, although the shortened treatment was substantially better than 4 sessions of an alternative psychosocial treatment, only 53% were panic free. Black et al.[18] attempted to reduce cognitive therapy to 8 sessions and also to alter the content of cognitive therapy somewhat and reported very high attrition and markedly inferior results, with only 32% of the sample panic free at the end of this time. Nevertheless, as is evident in the Gould et al.[10] meta-analysis, the overwhelming majority of studies report highly favorable results.

However, as is often the case, more recent analyses indicate that some of these results might be too optimistic. For example, at the Center for Anxiety and Related Disorders, we[25] followed patients treated with panic control treatment longitudinally rather than cross-sectionally. Re-

Table 2. Change in the Estimates of Long-Term Clinical Outcome as a Function of Various Cross-Sectional and Longitudinal Criteria*

Criteria	Meeting Criteria	
	Percent	N (of 63)
Cross-sectional		
Panic free at 24MFU	74.6	47
HES at 24MFU	57.1	36
Longitudinal		
HES at 24MFU + no further treatment for panic	47.6	30
HES at 3MFU and 24MFU	27.0	17
HES at 3MFU and 24MFU + no panics in past year	20.6	13
HES at 3MFU and 24MFU + no panics in past year + no further treatment for panic	20.6	13

*Data from reference 25. Abbreviations: 24MFU = 24-month follow-up; HES = high end-state functioning (based on criteria requiring no panic attacks in the past month and an Anxiety Disorders Interview Schedule-Revised [ADIS-R] clinical severity rating of 2 or less on a scale ranging from 0 [none] to 8 [very severely disturbing-disabling]); 3MFU = 3-month follow-up.

sults are presented in Table 2. While 74% of our patients remained panic free at a 24-month follow-up when followed cross-sectionally and 57% had reached a status of "high end-state functioning" that would represent a state close to "cured," these numbers dropped notably when patients were followed longitudinally. For example, if we require that patients achieve high end-state functioning status at the 24-month follow-up and have sought no further treatment for panic during that 2-year period, the percentage meeting criteria drops to 47.6%, with percentages dropping further as criteria are made more rigorous. Thus, it seems that at least some of these patients do reasonably well over the long term but continue to suffer from periods of exacerbation of their PDA.

Other studies have shown that it is very important to attend to any residual agoraphobic avoidance, since this avoidance does not remit on its own, no matter how mild, with successful resolution of panic attacks.[12] Other evidence suggests that agoraphobic avoidance may be the most significant predictor of long-term difficulties.[26]

Finally, my colleagues and I are in the midst of completing a multisite collaborative study testing the separate and combined effects of imipramine and panic control treatment on patients with PDA who have only mild agoraphobic avoidance. Preliminary results indicate that, although we have two effective treatments (drug and psychosocial), the psychosocial treatment is as good or better than medication and there is no particular advantage to the combination, at least in the short term. Completion of the study and further analyses will be required to bear this out. In addition, our collaborative group has begun plans for a long-term maintenance study encompassing patients with the full range of agoraphobic avoidance, which will incorporate new procedural developments in the administration of intensive in vivo exposure into standard panic control treatment. In addition, the medication that will be evaluated will be a serotonin selective reuptake inhibitor (SSRI) rather than imipramine, reflecting new developments in pharmacologic approaches. The expectation is that these combinations will lead to substantially better long-term results.

Drug names: fluvoxamine (Luvox), imipramine (Tofranil and others).

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Discussion

Cognitive-Behavioral Therapy

Dr. Charney: How important is the breathing retraining component of panic control treatment?

Dr. Barlow: Patients like breathing retraining. They find it useful and learn it quickly. Although we think breathing retraining makes the weakest contribution to changing patients' behavior, patients tend to attribute a lot of change to it.

Dr. Davidson: Are there any data on the percentage of patients who reject cognitive behavior therapy once they learn what it involves?

Dr. Pollack: In our ongoing study of patients with panic disorder, we discuss both medications and behavior therapy with each patient and ask them whether they would consent to be randomly assigned to either treatment. To date, nearly 90% of patients have a clear preference for one treatment or the other, and it appears to be equally distributed between drugs and cognitive behavior therapy. Only 1 in 10 patients is willing to accept randomization.

Dr. Barlow: One problem with cognitive behavior therapy is that most patients with panic disorder do not have access to the right type of treatment programs. When they do enter good behavioral programs, they respond well, but often these programs are not available.

Dr. Rosenbaum: Would patients respond if they received only some elements of the program, such as breathing retraining, rather than the formal package?

Dr. Marshall: One study of emergency department patients found that just telling patients experiencing their first panic attack to confront their fears might make a significant difference.

Dr. Ballenger: I am concerned about the difficulty of disseminating data on cognitive behavior therapy to physicians who are not psychiatrists.

Dr. Barlow: Another problem is that studies of cognitive behavior therapy have not provided data on the day-to-day improvement experienced by patients. In some of the drug studies, we have weekly data, which show that response can vary from week to week. If we had a rating of how much difficulty a patient had every day of the first 3, 6, or 12 months of treatment, we would have a more fair assessment of the patient's response.

Dr. Jefferson: That approach is becoming a reality. By using computers, physicians can have patients rate themselves on a daily basis from home using a touch-tone telephone.

Combined Cognitive Behavior and Drug Therapy

Dr. Barlow: Some of the skepticism about cognitive behavior therapy arises from data showing that only 27% of patients are well and stay well at every assessment point. The next step would be to study cognitive behavior therapy combined with drug treatment to determine whether this combination is better cross-sectionally and longitudinally in preventing the "blips" in the patient's response to treatment.

Dr. Rosenbaum: The issue of combination therapy is interesting. In many studies of cognitive behavior therapy, patients are allowed to remain on whatever medication they were taking before enrolling in the study. Thus, a substantial number of cognitive behavior studies are reporting efficacy not for cognitive behavior therapy alone, but for combination treatment. Would the outcomes have been different if the medication was not permitted?

Dr. Barlow: In our trials of cognitive behavior therapy, we allow patients to remain on their medication. Approximately 50% of patients are taking a drug prescribed by their primary care physician, and 90% of these patients are taking low, probably nontherapeutic doses of benzodiazepines. Typically these patients are prescribed 0.25 mg of alprazolam or the equivalent of clonazepam. Sometimes the dosing is on an as-needed basis.

Dr. Rosenbaum: It is possible, however, that the low-dose benzodiazepine may facilitate treatment or allow the patient to tolerate some of the initial interventions that might have caused them to drop out had they not been taking the drug.

Dr. Barlow: We need to study that issue further. However, at our clinic, there is no post-acute difference between patients taking low-dose benzodiazepines and those who do not. These results did not change even after cor-

recting for sample bias. However, in the long term, those taking low-dose medications do slightly worse, even after correcting for initial severity levels. We're not sure why.

Dr. Charney: Are there some aspects of panic attacks that cannot be controlled by cognitive behavior therapy?

Dr. Barlow: Limited symptom attacks do respond to cognitive behavior therapy. Patients who respond to this type of therapy have dramatic and full responses to it.

I wonder about the study showing a negative interaction between benzodiazepines and cognitive behavior therapy because this has not been our clinical experience in the short term. Part of it has to do with how the benzodiazepines are used. Probably the worst way to use them, from a behavioral point of view, is p.r.n. when the patient is having a panic attack. This limits the benefits of behavior therapy. The best approach might be to maximize the benzodiazepine treatment to provide good control of symptoms and then to add cognitive behavior therapy.

Dr. Rosenbaum: Does cognitive behavior therapy have the same potency in a patient with panic disorder and agoraphobia compared with one who has panic disorder alone?

Dr. Charney: We are looking at that question now. There might be something different biologically about these patients that caused them to become agoraphobic. The intensity of their panic or other underlying mechanisms might distinguish them from patients who have panic attacks but do not become agoraphobic.

Dr. Barlow: We looked at a number of variables in an attempt to identify patients prone to agoraphobia. Variables such as severity of the panic attack, place of onset of panic, and frequency of panic attacks were not related to agoraphobia. Our tentative conclusion was that agoraphobia was determined primarily by cultural and psychosocial factors. For example, the female sex bias in this disorder seemed to be related to a willingness to admit fear and a tolerance for being housebound. Conversely, male patients tend to deal with panic attacks by self-medicating, usually with alcohol. Our feeling is that agoraphobia is primarily related to psychosocial factors, although there may be some biological determinants.

Comorbid Disorders

Dr. Rapaport: Please comment on your comorbidity-morbidity data.

Dr. Barlow: We found that pretreatment comorbidity-morbidity did not affect a patient's post-acute or long-term outcome. The patients we studied had a principal diagnosis of panic disorder and were considered comorbid if they had another Axis-I disorder. Most of the patients had a mood disorder.

We noted an immediate general improvement with cognitive behavior therapy across the full range of psychopathology. During follow-up, the panic disorder continued to be controlled, but the other disorders would begin to return, even up to 2 years later. Thus, the results of cognitive behavior therapy appear to be specific for panic disorder.