

## INVITED ESSAY

# PSYCHOLOGICAL TREATMENT OF PANIC: WORK IN PROGRESS ON OUTCOME, ACTIVE INGREDIENTS, AND FOLLOW-UP

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**Summary**—Initial interest in the causes and treatment of panic disorder was triggered by biological theories and investigators. More recently, however, research on newly developed psychological approaches for panic has advanced our understanding of the disorder and has led to the development of specific treatment programs. Typically, these programs consist of a range of treatment components that more or less directly target panic attacks and the fears and behaviors associated with them. The paper reviews four studies evaluating these programs that have recently been completed or are close to completion in different centers in the United States (Albany, New York; Austin, Texas) and Europe (Oxford, England; Marburg, Germany). Conforming to strict methodological standards, these studies report consistently high success rates and temporal stability of the treatment gains. About 80% or more of the patients receiving combined cognitive-behavioral treatments achieved panic free status as well as strong and clinically significant improvement in general anxiety, panic-related cognitions, depression, and phobic avoidance. Furthermore, these gains were maintained at follow-ups of up to 2 years. The success of these psychological treatments compares favorably with the outcome for the established pharmacological treatments. In addition, the studies provide new insights into the active ingredients that may operate in cognitive-behavioral treatments for panic disorder and show the feasibility of group treatments. Together, these studies underscore the fact that cognitive-behavioral treatments rest on firm experimental evidence that justifies their application in everyday practice as well as continued research into their mechanisms of action.

## INTRODUCTION

Over the past decade, panic attacks have become a major focus of psychopathology and treatment research. Two major reasons for this development are new etiological theories and alarming epidemiological data. Large scale community studies show that even when conservative diagnostic criteria are used, about 10% of the general adult population experience at least occasional panic attacks (Myers, Weissman, Tischler, Holzer, Leaf, Orvaschel, Anthony, Boyd, Burke, Kramer & Stoltzman 1984; Robins, Helzer, Weissman, Orvaschel, Gruenberg, Burke & Regier, 1984; Angst & Dobler-Mikola, 1985; Lee, Kwak, Rhee, Kim, Han, Choi & Lee 1985; Yeh, Hwu, Chang & Yeh, 1986; Wittchen, 1988). In about 5% of cases these attacks are so frequent and disabling that the DSM-III-R criteria (American Psychiatric Association, 1987) for panic disorder with or without agoraphobia are fulfilled. Although the course of the disorder can fluctuate, the long-term prognosis without adequate treatment is worse than for major depression (Schapira, Kerr, & Roth 1972; Coryell, Noyes & Clancy, 1983; Wittchen, 1988). A high frequency of secondary problems such as alcoholism, drug abuse, and severe depression has been well established (see Barlow & Shear, 1988). These problems further limit the quality of life and undermine the patients' self-efficacy, thus making them even less able to confront their anxiety. In many cases, this leads to a downward spiral resulting in significant impairment and intensive suffering for the patients and their relatives. The severity of the disorder and its consequences may be responsible for the fact that panic disorder patients seek professional treatment more frequently than patients with any other mental disorder (Boyd, 1986). Taken together, these facts clearly show that panic disorder is a major health care problem.

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A second impetus for the increased interest in panic disorder came from biological theories of the origin and treatment of panic disorder (e.g., Klein, 1981; cf. Margraf, Ehlers & Roth, 1986a; Margraf & Ehlers, 1990). In part as a reaction to these theories, new psychological approaches have more recently been proposed and tested. Today, many authors give panic attacks a prominent role in the classification, etiology, and treatment of anxiety disorders. A particularly intriguing problem for researchers and clinicians alike is the apparent "spontaneity" of many attacks. The fact that most patients insist that at least some of their attacks come "out of the blue" without any danger or sufficient reason to panic, has posed a major challenge to basic research and clinical management. Most psychological explanations have relied on internal cues as triggers for "spontaneous" attacks. Such internal cues typically are bodily sensations such as palpitations, dyspnea, or dizziness that easily lend themselves to misinterpretation as signs of imminent physical or mental dangers. The dangers anticipated by panic patients are of a catastrophic nature and center around the fears of dying, going crazy, or losing control (the latter with possibly further catastrophic consequences). Formulated more generally, a number of recent psychological or psychophysiological models (e.g. Barlow, 1986, 1988; Clark, 1986, 1988; Margraf, Ehlers & Roth, 1986b; Salkovskis, 1988; Ehlers & Margraf, 1989) explain panic attacks as the consequence of a positive feedback loop between the perception of internal cues (bodily sensations or, less frequently, mental processes), their association with threat, and the patient's anxiety response to these symptoms which in turn leads to further bodily sensations (see Margraf & Ehlers, 1989). The research on these psychological models has advanced our understanding of panic disorder (for overviews see Rachman & Maser, 1988; Margraf & Ehlers, 1989; McNally, 1990) and has led to the development of specific programs for the treatment of panic attacks even in the absence of phobic avoidance behavior.

Usually, these treatment programs consist of several components that more or less directly target panic attacks and the fears and behaviors associated with them. The behavioral components typically include not only exposure to feared situations (e.g. by using public transportation or going to shopping malls) but also exposure to bodily sensations (e.g. by hyperventilation or exercise). Among the most important cognitive techniques are identifying and challenging misinterpretations of bodily sensations by careful examination of the patient's evidence and additional data if needed. The first published evidence for the efficacy of specific cognitive-behavioral treatment programs for panic has come from a number of case series and uncontrolled studies (Barlow, Cohen, Waddell, Vermilyea, Klosko, Blanchard & Di Nardo, 1984; Waddell, Barlow & O'Brien, 1984; Clark, Salkovskis & Chalkley, 1985; Gitlin, Martin, Shear, Frances, Ball & Josephson, 1985; Kopp, Mihaly & Vadasz, 1986; Salkovskis, Jones & Clark, 1986; Sokol, Beck, Greenberg, Wright & Berchick, 1989; Michelson, Marchione, Greenwald, Glanz, Testa & Marchione, 1990; Shear, Ball, Fitzpatrick, Josephson, Klosko & Frances, 1991). Each of these publications reported very substantial positive outcomes that, when studied, appeared to be stable across follow-ups that lasted up to 2 years. Additional published evidence comes from controlled studies (Barlow *et al.*, 1984; Öst, 1988; Barlow, Craske, Cerny & Klosko, 1989; De Ruiter, Rijken, Garssen & Kraaimaat, 1989; Klosko, Barlow, Tassinari & Cerny, 1990). Although these results look very promising, the preliminary nature of most of the studies on which they are based has to be acknowledged. The compound nature of the treatment programs makes it impossible to determine which components contribute to success and to identify the mechanisms of action. In addition, the evidence for the durability of the successes is still very limited.

Given the seriousness of panic disorder as a health care problem and the current debate on its treatment (cf. National Institute of Health Consensus Development Conference Statement), it is of considerable interest to know that a number of additional studies have recently been completed or are close to completion in different centers in the United States and Europe that address these issues using adequate control groups and sample sizes as well as comprehensive assessments. The present paper therefore aims to review these studies and their preliminary findings as they were presented at a recent symposium at the *25th Annual Convention of the Association for Advancement of Behavior Therapy*. More specifically, the studies reviewed here represent an attempt to answer the following three questions:

- (1) How successful are different psychological treatment programs involving behavioral, cognitive, and panic inoculation approaches?

- (2) How good are the long-term outcomes of cognitive-behavioral treatments for panic disorder?
- (3) What are the active ingredients or mechanisms of action that lead to therapeutic success?

All studies share these important methodological features:

- (i) Careful diagnosis of panic disorder and other psychopathology. The diagnosis of panic disorder was always established by specially trained clinicians using structured interviews (either the Anxiety Disorders Interview Schedule—Revised (ADIS-R), (DiNardo & Barlow, 1990), or the Structured Clinical Interview for DSM (SCID), (Spitzer, Williams & Gibbon, 1987).
- (ii) Control groups (wait list, components of cognitive-behavioral packages, or other treatments).
- (iii) Random assignment to treatment conditions.
- (iv) Multimethod assessment of treatment outcome.
- (v) Adequate sample sizes.
- (vi) Assessment of treatment integrity.
- (vii) Inclusion limited to patients with active panic disorder (no partially remitted cases).

#### ALBANY STUDY

(BARLOW, BROWN, CRASKE, RAPEE & ANTONY, 1991; BARLOW *et al.*, 1989; CRASKE, BROWN & BARLOW, 1991)

Barlow *et al.* (1989) compared a wait list condition to three active treatment conditions: (1) progressive muscle relaxation, (2) panic control treatment consisting of interoceptive exposure and cognitive restructuring, and (3) a combination of progressive muscle relaxation and panic control treatment. A detailed description of panic control treatment was provided in a treatment manual by Barlow and Cerny (1988). A total of 56 patients participated in the study. Mean ages for the four patient groups varied between 32 and 38 yr and the proportion of female patients ranged from 67 to 93%. All three treatments resulted in significantly more improvement than the wait list condition on a variety of outcome measures (including State-Trait Anxiety Inventory, Beck Depression Inventory, Marks & Mathews Fear Questionnaire, Hamilton Anxiety and Depression Rating Scales, frequency of panic attacks) and a composite measure of endstate functioning. Additionally, the two conditions employing panic control treatment led to significantly more panic-free patients at the end of treatment in comparison to progressive muscle relaxation and the wait list. The new results presented in Craske *et al.* (1991) show that at follow-ups 6 and 24 months after the end of treatment, a significantly greater percentage of panic control treatment and combined treatment patients were panic-free than were progressive muscle relaxation *Ss*. The same pattern emerged when the percentage of *Ss* classified as high endstate functioners was analyzed. At 24-months follow-up, the percentage of panic-free patients was 35.7, 81.3 and 42.9% for the progressive muscle relaxation, panic control treatment and combined treatment groups, respectively (these percentages include dropouts with the assumption that dropouts continued to panic). Thus, all treatment groups evidenced maintenance of treatment gains and on some measures there was even further significant improvement (e.g. trait anxiety). However, no group differences emerged in the percent of *Ss* achieving high endstate functioning at this point. This finding is partly attributable to continuing agoraphobic avoidance in some of the patients despite the absence of panic attacks. Duration of disorder, age, gender, use of medication and depression scores at the end of treatment did not relate significantly to panic-free status or endstate status at either follow-up period.

In an additional dismantling study that is nearing completion, the relative efficacy of adding interoceptive exposure, breathing retraining, or both is being examined in 81 patients with panic disorder with no or mild agoraphobic avoidance. Preliminary analyses of post-treatment and 3-month follow-up interview (ADIS-R) and questionnaire data indicate a general equivalence in treatment response across the four conditions (e.g. percent panic-free, percent achieving high endstate status). Nevertheless, initial evidence suggests that, on some process-type measures (e.g. response to CO<sub>2</sub> inhalations), the two conditions receiving the component of interoceptive exposure

tended to show greater change. It will be of great interest to determine whether post-treatment responses on these types of measures (i.e. biological challenge indices) have utility in predicting long-term clinical outcome.

#### MARBURG STUDY (MARGRAF & SCHNEIDER, 1991)

Two major candidates for “active ingredients” of modern psychological treatments for panic disorder are reattribution of anxiety symptoms and habituation due to exposure. To investigate their contribution to treatment success, Margraf and Schneider (1991) compared pure cognitive therapy (no exposure to external or internal anxiety-inducing cues) to pure exposure treatment (no reattribution of anxiety symptoms), combined cognitive/exposure treatment, and a wait list control condition. The combined treatment was described in a detailed manual by Margraf and Schneider (1989). All treatments focused directly on panic attacks or the stimuli and cognitions associated with them. In addition, process measures were monitored and their relationship to therapeutic outcome studied. These measures were either non-specific (therapist–patient relationship, therapist competence and directivity, treatment credibility, patient expectancy), or specific with respect to panic disorder (self-exposure, specific cognitions). All 82 patients met DSM-III-R criteria for panic disorder with a primary complaint of “spontaneous” panic attacks and were not taking any psychotropic medication while in the study (controlled by blood screens for benzodiazepines, tricyclics, and beta-blockers). Mean duration of the disorder was 7 years with a minimum of 1 year in order to exclude recent onset cases which might be suspected to represent “easier” cases and therefore inflate success rates.

Systematic analyses of tape recordings of therapy sessions showed that treatment integrity was maintained in all three treatment conditions. Preliminary analysis of outcome revealed strong positive effects on all measures including panic and self-exposure diaries, clinical ratings by patients and therapists, clinical questionnaires, ambulatory psychophysiological monitoring (48 hr), and response to CO<sub>2</sub> panic induction (15 min of 5% CO<sub>2</sub>). The fact that no improvement was observed during a 4-week pre-treatment baseline as well as the lack of significant changes in the wait list condition support the interpretation that improvements were true treatment effects. Treatment successes were stable at a first 1-month follow-up when 77–93% of all patients in the three treatment conditions were completely panic-free (5% in the wait list condition, based on self-monitoring data). While the vast majority of the patients had been taking psychotropic medication before entering the study, no patient did so at the 1-month follow-up. Overall, drop-out rates were low with a minimum of 0% in the combined treatment (14 and 20% in the pure cognitive and exposure conditions, respectively). Other than the difference in drop-out rates, there were hardly any significant differences between the three active treatment conditions. This makes the interpretation of the process measures even more important.

Using the specific process measures, a strong relationship was identified between treatment success and panic-specific cognitive changes; however, the amount of self-exposure apparently had no influence on outcome. Regarding the non-specific process measures, significant positive relationships were noted between success and a good therapeutic relationship, high treatment credibility, and high therapist competence and directivity. The magnitude of these correlations, however, was only moderate. Although a definite conclusion is not yet possible, it can be argued that the data support the role of reattribution more than that of habituation.

#### OXFORD STUDY (CLARK, SALKOVSKIS, HACKMAN & GELDER, 1991)

Cognitive therapy of panic disorder, as developed by the Oxford group (which includes behavioral experiments including a small amount of interoceptive exposure), has been shown in several case series to be effective (cited in the introduction). However, relatively little is known about its long-term outcome and how it compares to other empirically validated treatments of panic. In order to investigate these questions, 64 patients meeting the DSM-III-R criteria for panic

disorder without severe agoraphobic avoidance were randomly assigned to either cognitive therapy, applied relaxation (a specific relaxation technique in conjunction with graded exposure to feared situations developed by Öst, 1987), imipramine (mean = 233 mg/day verified by blood levels), or a wait-list. Descriptions of cognitive therapy for panic were published by Clark (1989) and Salkovskis and Clark (1991). Cognitive therapy and applied relaxation patients were seen weekly for 3 months, as were patients given imipramine. In addition, imipramine patients were maintained at a maximum dose for a further 3 months before being gradually withdrawn; patients in the two other treatment conditions were allowed up to three booster sessions during this time. All three treatment groups received weekly self-exposure to feared situations. Outcome measures included patient and blind assessor ratings of panic frequency and severity, panic diaries, Beck Anxiety and Depression Inventories, Hamilton Anxiety Rating Scale, laboratory psychophysiological assessments, ambulatory monitoring, and measures assessing catastrophic misinterpretations.

Immediate post-treatment results indicated that cognitive therapy was significantly more effective in reducing panic, generalized anxiety, panic-related cognitions, and avoidance than were applied relaxation or imipramine, which in turn were more effective than no treatment. After 3 months of treatment, 90% of the patients in the cognitive condition were panic free. This compared to 50% in the applied relaxation, 55% in the imipramine, and 7% in the wait list conditions. To investigate long-term outcome, almost all (96%) patients were reassessed 12 months after the end of treatment. Again the same pattern of results emerged. At follow-up, cognitive therapy was still significantly better than the comparison treatments. Moreover, patients treated with imipramine were significantly more likely to relapse and require further treatment than were patients treated with cognitive therapy (40 vs 5%). One year after the end of treatment, 80% of the patients in the cognitive condition were still panic free without having required any additional treatment. This compared favorably to the values obtained with applied relaxation (47%) or imipramine (50%). In addition, an analysis of potential predictors of long-term outcome revealed that measures of misinterpretation of bodily sensations, taken at the end of treatment, correlated positively with symptomatology at follow-up. This relationship was independent of the degree of symptomatology measured at the end of treatment.

#### AUSTIN STUDY

(TELCH, 1991)

The major aim of this controlled clinical trial was to investigate the efficacy of psychological panic control procedures administered in a group format. Sixty-seven panic patients with minimal or no agoraphobic avoidance were matched on panic severity (as determined by the SCID) and randomly assigned to receive either group panic inoculation training or a delayed treatment control condition. Panic inoculation training consisted of twelve 90-min sessions over an 8-week period. Treatment was administered in small groups with group sizes ranging from 4 to 6 patients. The content of panic inoculation training consisted of the following major components: (1) information concerning the nature and physiology of anxiety, (2) cognitive interventions aimed at the identification and alteration of inaccurate beliefs that trigger panic, (3) interoceptive exposure aimed at normalizing heightened emotional responses to benign somatic cues, and (4) respiratory training aimed at increasing perceptions of control over respiratory responses and arousal in general. A comprehensive assessment battery tapping the major clinical dimensions of panic disorder was administered at baseline, post-treatment, and 6-months follow-up. Assessments included measures of panic frequency and expectancy, anxiety, "fear of fear", depression, agoraphobic avoidance, response to a hyperventilation challenge, and global functioning. At baseline, the two treatment groups did not differ on any of the major clinical or demographic measures.

At the end of treatment, however, the results indicated a marked reduction on all indices of symptomatology in those patients who received panic inoculation training. In contrast, the untreated patients showed no significant improvement on any of the outcome measures. The proportion of panic-free patients was 85 and 83% in the treated group at post-treatment and follow-up, compared to 30% in the control group (no untreated follow-up data were available for the control group). There was no effect of medication status on treatment outcome. The clinical significance of the treatment gains was assessed by examining the proportion of patients reaching

scores in the normal range with respect to panic attacks, anxiety, phobic avoidance, fear of fear, and depression. At post-treatment, the average rate of recovery across these five clinical outcome domains was 81% for the panic inoculation patients and only 31% for the control patients. Treatment success was stable as shown by an average recovery rate of 79% in the treated patients 6-months after the end of treatment. The results of this study demonstrate the efficacy of a group-administered psychological treatment for panic disorder.

## DISCUSSION

Although these studies come from different centers in the United States and Europe, their results reveal a high degree of consistency in demonstrating the efficacy of treatments combining cognitive and behavioral interventions. Conforming to strict methodological standards, the present studies established high success rates and temporal stability of the treatment gains. 80% or more of the patients receiving combined treatment conditions achieve panic-free status as well as strong and clinically significant improvement on other dimensions of the disorder such as general anxiety, fear of fear, depression, and phobic avoidance. On the average, these successes remained stable over the follow-up periods investigated which lasted as long as 1–2 yr in the Albany and Oxford studies.

In addition to establishing global success, the studies also provide new insights into the active ingredients that may operate in cognitive-behavioral treatments for panic disorder. The more modest results achieved in treatment conditions based primarily on relaxation indicates that this technique is probably not the optimal intervention for panic disorder, a conclusion that is reached by both groups that investigated relaxation techniques (Albany and Oxford studies). The Marburg study shows that therapist-guided exposure to feared stimuli (internal or external) is not a necessary component of successful treatment in patients with a primary complaint of panic attacks although there are some indications from other studies that avoidance behavior, if present, may need to be targeted separately from panic attacks (cf. Brown & Barlow, 1992; Craske *et al.*, 1991). The analysis of the self-exposure data sheds further doubt on the necessity of exposure. On the other hand, full-scale therapist-guided cognitive interventions also do not seem to be necessary components. Here, however, the analysis of the process measures revealed consistent significant relationships between cognitive changes and treatment success that were observed even in the “pure” exposure condition. In this study, the major advantage of the combined treatment was its capacity to prevent drop-outs which occurred significantly more often in the single component treatments. This is in line with the finding of the Albany study that the greatest success was achieved by the complete panic control treatment package. The success rates of the combined treatments in these two studies are very close to those obtained by cognitive therapy condition in the Oxford study and by the panic inoculation condition in the Austin study.

The success of the psychological treatments employed here compares favorably with the outcome for the established pharmacological treatments. The direct comparison with imipramine given at an adequate dosage over sufficient time in the Oxford study yielded a result comparable to that published by Klosko *et al.* (1990). In their study, panic control treatment resulted in 87% panic-free patients compared to 50% for a trial of alprazolam treatment. Whereas this study investigated only short-term outcome, the Oxford study presented above shows that comparable differences are obtained with respect to long-term success. The relapse rates after cognitive-behavioral treatment are considerably lower than those obtained with the pharmacological alternatives studied thus far. The stability of the treatment gains is of major importance for cost–benefit considerations. This is also true for the format in which the treatments are administered. The Austin study is the first to show major success with a highly cost-effective group treatment for panic disorder. The outcome achieved here was comparable to that in the other studies, a fact that merits further attention and study.

Together, the studies reviewed here show that we are no longer dealing with experimental treatments that still have to prove themselves. Instead, cognitive-behavioral treatments rest on firm experimental evidence that justifies their application in everyday practice. Nevertheless, continued research is needed in order to maximize their cost-effectiveness and to learn more about the mechanisms involved in therapeutic change resulting from these interventions.

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