CLASSIC ARTICLE

One reason for choosing this paper by Klosko et al.[1] as the classic article for a journal focused on psychotherapy practice and research is that it contributes to an area of much current interest: the relative effectiveness of psychosocial and psychopharmacological therapies. A second reason is that the study compares cognitive-behavioral therapy and alprazolam, both state-of-the-art treatments. The third reason is that the study is directed toward a common and often disabling psychopathological entity, panic disorder, the treatment of which is currently undergoing intriguing changes.

For many years, two relatively independent lines of research addressed what we now call panic disorder with or without agoraphobia—lines of research that viewed the disorder rather differently. Research in behavior therapy, beginning with studies of systematic desensitization,[2] focused on the phobic aspects of the disorder, whereas research in psychopharmacology focused on panic as the primary aspect of the psychopathology of the condition.[3] The work in behavior therapy eventually established that the effective therapeutic procedure was exposure to the feared situation, a procedure effective across all the phobias.[4,5] Parallel with these developments, psychopharmacological studies established the effectiveness of imipramine and other antidepressants in reducing both panic and the related phobias.[6,7] The different views of the disorder and the different assessment procedures deriving from the two research perspectives resulted in some confusion and controversy concerning both the relative effectiveness and the mechanisms of action of the two different treatment approaches.

Eventually it was realized that the combination of imipramine and exposure therapy was probably the most appropriate treatment approach for individuals with panic and some degree of agoraphobia.[6,7] The research findings also led most workers in the field to regard panic as the first element in the sequence of developing the full-blown syndrome, which includes agoraphobia and the other phobic avoidances. It also became evident that these individuals showed characteristic distorted thinking patterns involving the misinterpretation of bodily feelings as denoting an impending serious physical or mental illness or an impending loss of control. The focus on the importance of panic, combined with the delineation of the cognitive distortions characterizing the syndrome, led several researchers to begin developing a cognitive-behavioral treatment for panic.[8] Once again, in parallel with this development, a new and potent medication, alprazolam, was shown to be effective in this disorder.[9]

The focus of cognitive-behavioral therapy for panic disorder is on the specific distortions in thinking that characterize the patient's misperceptions of the dangerousness of certain bodily sensations. For example, a patient might rise from a sitting position and notice a change in his or her heart rate and perhaps momentary dizziness. These events may be misinterpreted as an impending heart attack, resulting in the development of anxiety and the exacerbation of the crucial bodily feelings denoting a heart attack, resulting in a full-blown panic attack. Such misinterpretations are felt by cognitive theorists to provoke many, if not all, panic attacks. If this interpretation of the development of a panic attack is correct, then it should be possible to prevent the development of full-blown panic attacks by changing the patient's distorted

thinking patterns. Hence, cognitive-behavioral therapy first involves identifying and clarifying the bodily feelings and distorted cognitions that lead to anxiety. This sequence of events and the faulty conclusions drawn by the patients are then challenged both by logic in the therapy session and by behavioral experiments aimed at exacerbating the crucial bodily sensations and proving that the feared consequences do not occur. Eventually, the patient can learn to identify the distorted thinking pattern very early in the sequence and prevent the development of further anxiety, thus reducing the frequency of panic attacks.

In the study by Klosko et al., this core therapeutic element was accompanied by respiration training to slow down breathing and by relaxation training to further diminish anxiety. This cognitive-behavioral therapy was compared in a randomized study with alprazolam, placebo, and a waiting-list condition. The study has much to recommend it, particularly the use of a well-developed manual that is available to researchers and clinicians for replication of the behavior therapy in further studies and for use in the clinic. The assessment procedures were state of the art, strengthening confidence in the conclusions that might be drawn from the study. There are also aspects of the study that are imperfect. As in most single-site studies, the sample size is fairly small and is likely to be inadequate for the comparison of two active treatments. Furthermore, although alprazolam appeared to be administered competently, active medication was not significantly different from either the cognitive-behavior therapy or placebo, probably because of the small sample size involved. Overall, we can conclude from this study that cognitive-behavioral therapy is more effective than a placebo condition and is at least as effective as alprazolam in the treatment of panic disorder.

Two further controlled studies of cognitive-behavioral therapy for panic disorder have appeared since the publication of this classic article. In one of these studies, cognitive therapy was found to be more effective than brief supportive psychotherapy.[10] In the other study,[11] cognitive-behavioral therapy was found to be more effective than a delayed treatment control group. Perhaps most impressive is that in two of these studies[1,10] 87% of the patients were panic free at the end of treatment, and in the third study 85% of patients were panic free.[11] These three studies taken together suggest that the cognitive-behavioral approach to the treatment of panic disorder is effective and may be a first-line treatment approach for selected patients. Further studies, looking at both short-term and long-term results, are now needed to determine the best sequencing of pharmacotherapy and cognitive-behavioral therapy. Such studies will undoubtedly necessitate multicenter efforts to achieve an adequate sample size. Studies such as that by Klosko et al.[1] are the building blocks upon which such multicenter studies rest.

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A Comparison of Alprazolam and Behavior Therapy in Treatment of Panic Disorder

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The results of a clinical outcome study (N = 57) comparing behavior therapy directed at panic disorder (panic control treatment [PCT]) with alprazolam were reported. These conditions were compared with a medication placebo and a waiting-list control group. Patterns of results on measures of panic attacks, generalized anxiety, and global clinical ratings reveal that PCT was significantly more effective than placebo and waiting-list conditions on most measures. The alprazolam group differed significantly from neither PCT nor placebo. The percentage of clients completing the study who were free of panic attacks following PCT was 87%, compared with 50% for alprazolam, 36% for placebo, and 33% for the waiting-list group. Since alprazolam may work more quickly than PCT but may also interfere with the effects of behavioral treatment, these data suggest a series of studies on the feasibility of integrating these treatments and on the precise patterns and mechanisms of action of various successful treatment approaches to panic disorder.

Recently a large-scale, multicenter study examined the effectiveness of alprazolam for panic disorder (Ballenger et al., 1988). In that study, over 500 patients were assigned randomly to alprazolam or placebo. Assessment measures included prospective self-monitoring of panic attacks. The study yielded a complex pattern of results, but the central finding was that 55% of alprazolam subjects and 32% of placebo subjects who began the study were panic-free following 8 weeks of treatment or at the time they dropped out (endpoint analysis). Because a significantly larger number of placebo subjects dropped out (44% of those placebo subjects who completed at least 3 weeks of treatment dropped out before Week 8 compared with 8% of alprazolam subjects), an analysis of those who completed the 8- week study was also reported. Of those subjects who were completers, 59% of alprazolam subjects were free of panic versus 50% of placebo subjects, a nonsignificant difference. Because the latter result may favor placebo by highlighting placebo responders and because the former result may favor alprazolam by underestimating the number of placebo subjects who might have responded if they had stayed in treatment, Ballenger et al. suggested that the true effects of alprazolam fall somewhere between these two methods of reporting results.

Several investigators have reported uncontrolled clinical replication series that suggest the effectiveness of behavioral or cognitive-behavioral treatments targeting panic attacks directly rather than agoraphobic avoidance (e.g., Clark, Salkovskis, and Chalkley, 1985). In these uncontrolled reports, from 80% to 100% of clients were free from panic after treatment. In two prelimi-

nary controlled studies of behavioral treatments for panic disorder (Barlow et al., 1984; Beck, 1988), clients improved significantly more than waiting-list controls. Now the results from a large-scale treatment outcome study of panic disorder are available (Barlow, Craske, Cerny, and Klosko, 1989). In that study, a newly developed treatment for panic disorder focusing on exposure to somatic sensations associated with panic attacks was evaluated. This exposure procedure, combined with cognitive therapy directed at catastrophic thoughts associated with panic attacks, was compared with a relaxation condition in which clients were taught to use relaxation in a cue-controlled manner whenever they began to feel anxious or panicky. In a third condition, these two treatments were combined. All three conditions were compared with a waiting-list control. Results indicated that over 87% of those who completed treatment and received exposure to somatic sensations plus cognitive therapy, either alone or in combination with relaxation, were free of panic attacks during a 2-week period after treatment. This compares with 60% in the relaxation condition and 35% in the waiting-list control group. Only those groups receiving exposure plus cognitive therapy were significantly different from waiting-list control subjects. However, a significantly greater number of subjects dropped out of the relaxation condition. Therefore, if one includes dropouts in the final analysis, the percentage of patients who were panic-free remains at approximately 80% in the exposure plus cognitive therapy conditions but drops to 40% in the relaxation condition, which is not significantly different from the waiting-list control group.

In view of the effectiveness of this behavioral approach and of alprazolam for panic attacks, the purpose of this study is to evaluate the relative effectiveness of each treatment in one setting using a group of clients diagnosed in an identical manner with outcome measured in precisely the same way. Both medication and placebo as well as a waiting-list group were included to provide benchmarks against which to assess therapeutic improvement. This study was seen as a precursor to studying possible integration or coordination of these treatments in panic disorder patients.

METHOD

Subjects

Our subject selection, exclusionary criteria, and general procedures followed closely the detailed protocol developed for the Upjohn cross-national study on panic disorder (Ballenger et al., 1988). Subjects between 18 and 65 years of age were drawn from the pool of patients presenting to the Phobia and Anxiety Disorders Clinic of the Center for Stress and Anxiety Disorders at the State University of New York at Albany. Although most panic disorder patients who qualified for the study presented with no more than mild agoraphobic avoidance, several with moderate to extensive agoraphobic avoidance were included.

Each patient was administered the Anxiety Disorders Interview Schedule–Revised (ADIS-R; Di Nardo et al., 1988), a structured interview that has been shown to be a reliable instrument for diagnosing panic disorder (Barlow, 1988). The ADIS-R administrators were advanced clinical psychology graduate students and postdoctoral or licensed clinical psychologists. All had completed extensive training that culminated in requiring trainees to match the diagnoses of experienced interviewers on 3 consecutive patients who were seen by both the trainees and the experienced interviewer. Each patient received a primary diagnosis of panic disorder, with a clinician's severity rating of at least 4 on a 0–8 scale in which 0 = *none*, 4 = *definitely disturbing/disabling*, and 8 = *very severely disturbing/disabling*. Thus subjects not only had to meet the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III; American Psychiatric Association, 1980) definition for a case but also had to present with at least moderate

severity. Only subjects who were panicking actively were included; that is, subjects who reported at least one panic attack in the week before starting treatment on the weekly record self-monitoring form (described later). Finally, subjects were between 18 and 65 years of age.

Exclusion criteria. Subjects were excluded who had begun pharmacotherapy or psychotherapy in the past 6 months; subjects who had been either in drug or psychotherapeutic treatment more than 6 months were excluded unless they agreed to stop such treatment for the duration of the study. Subjects were excluded who had been on 4 mg or more of alprazolam for any 3-week period and were nonresponders, who displayed evidence of benzodiazepine hypersensitivity or who had undergone cognitive-behavioral therapy for anxiety at any time. Exclusionary criteria also included (a) females who were pregnant or lactating or at risk to become pregnant; (b) subjects with significant medical problems, as determined by history, medical report, and laboratory values; (c) subjects with a history of psychotic disorder or dementia; (d) subjects with a history of alcohol or other substance abuse within the last 6 months; and (e) subjects with current or past bipolar disorder. Subjects with major depression were excluded only if depression predominated over panic disorder at the time of presentation and if depression predominated over panic disorder chronologically. Subjects with acute suicidal ideation were excluded.

Measures

Psychophysiological, clinical assessment, and medical assessment measures were administered to all subjects before and after treatment. Self-monitoring measures were administered throughout treatment. Psychophysiological measures and results are reported elsewhere (Klosko, 1987).

Self-monitoring measures. Subjects engaged in daily self-monitoring with the weekly record, a form constructed by clinic staff over a period of years with the goal of providing the most useful information about panic attacks while ensuring maximum compliance (see Barlow and Cerny, 1988). Subjects were instructed to record on the diary the following information about each discrete episode of anxiety experienced that day rated 4 or higher on the 0–8 scale: (a) date and time of onset and offset of the anxiety episode, (b) maximum level of anxiety during the episode, (c) whether the subject considered this episode of anxiety a panic attack (in accord with the revised edition of the DSM-III [DSM-III-R; American Psychiatric Association, 1987], subjects were instructed and trained to define a panic attack as the sudden onset of intense fear, accompanied by at least four characteristic panic symptoms; the attack had to peak within 10 min), and (d) whether the subject usually considered the situation or context in which the episode occurred to be anxiety provoking or non–anxiety provoking (in other words, was the episode situational or cued?).

Data from self-monitoring served to measure anxiety episodes and panic attacks, both spontaneous and situational. Because subjects were trained to separate panic attacks from episodes of anxiety that began more slowly and typically lasted longer, this procedure ensured a conservative measure of panic. Spontaneous attacks were defined as those that occurred in situations that subjects customarily rated as non-anxiety provoking; situational attacks occurred in situations that subjects customarily rated as anxiety provoking. Subjects were instructed to define *anxiety provoking* in relative fashion: a crowded grocery store might not produce anxiety for most people but might well produce anxiety for the particular subject.

Clinical assessment measures. Clinical assessment measures from the ADIS-R (Di Nardo et al., 1988) included global clinical severity

ratings, panic ratings, the Hamilton Anxiety Rating Scale, and the Hamilton Rating Scale for Depression.

Medical assessment and procedures. The study psychiatrist obtained medical histories from all subjects and administered a brief physical examination, which consisted of a medical history, vital signs, and examination of head and neck, chest, abdomen, extremities, skin, and neurological signs. If a more thorough physical examination was warranted, the subject was referred to an appropriate physician. Pretreatment and posttreatment blood samples were obtained from subjects in the three treatment groups (alprazolam, placebo, and cognitive-behavioral therapy) for clinical laboratory determinations of medical exclusion criteria as well as pretreatment and posttreatment plasma benzodiazepine screens.

Subjects in the three treatment groups withdrew from prestudy medications under the supervision of the study psychiatrist. Adherence to drug withdrawal was determined by analyses of plasma benzodiazepine screens. Subjects remained off medication for at least 7 days before administration of psychophysiological, self-report, and self-monitoring measures and random assignment to one of the three treatment groups.

Treatment

Alprazolam and placebo treatment groups. Subjects received 15 individual treatment sessions in weekly meetings with a study psychiatrist experienced in alprazolam treatment of panic disorder. Medication was supplied by the Upjohn Company in matching 1-mg tablets, packaged in matching bottles containing sufficient medication for 1 week, and was administered double-blind.

Treatment followed the protocol used in the Upjohn multicenter trial (Ballenger et al., 1988), adapted to 15 weeks. Medication was gradually increased following a standardized but flexible schedule until maximum benefit was achieved or dose-limiting side effects occurred. At least three attempts were made to titrate the medication upward to at least 6 mg per day. Dosage was advanced to a maximum of 10 mg per day if required. (See Ballenger et al., 1988, for a more detailed description of drug dose and regimen procedures.) The psychiatrist was instructed to limit interactions with subjects to discussion of clinical history, explanation of panic disorder, discussion of medication effects and side effects, and general support.

At the beginning of the 13th week of treatment, the psychiatrist began to taper doses of medication at a rate no faster than one tablet every 3 days. The psychiatrist continued meeting with subjects until they had stopped taking medication completely or, if they were unable to withdraw from medication, until they were restabilized on the study medication once again. At this point treatment was considered to be over, and the psychiatrist completed the poststudy termination record. If subjects wished to continue medication use, they were given appropriate referrals.

Behavior therapy treatment group. Subjects received 15 individual sessions of an integrated cognitive-behavioral treatment for panic disorder (panic control treatment, PCT) in weekly meetings. Therapists were either Ph.D. psychologists or advanced doctoral students who had been trained in the application of the treatment by observation and practice with corrective feedback. A detailed treatment manual was used, and supervision was provided on a weekly basis to ensure the correct application of therapeutic procedures. Treatment comprised a rationale and education about panic disorder and emphasized exposure to interoceptive (somatic) cues; cognitive approaches, progressive relaxation training, and respiration training (to slow breathing rate) were also included. (The detailed session-by-session treatment protocol is presented in Barlow and Cerny, 1988; an updated protocol suitable for distribution to clients for use under clinical supervision is

now available from the Center for Stress and Anxiety Disorders, State University of New York at Albany.) All therapy sessions were tape-recorded and checked for treatment integrity.

Waiting-list control group. Subjects were placed on a 15-week waiting list for treatment. They were told that they might contact the clinic by telephone during this time if they felt the need and that we would contact them approximately weekly by telephone. Although inclusion criteria required all subjects to have been stabilized on medication, waiting-list subjects were not required to withdraw from medication. Therefore, this waiting-list group might also be considered a minimal treatment condition, thereby providing a more conservative comparison with other treatment conditions.

Treatment integrity. The integrity of treatment delivery was examined by means of ratings of the content of 25% of PCT sessions. (All PCT sessions were audiotaped.) All drug treatment sessions were directly observed and rated. For PCT sessions, verbalizations were checked as belonging to one of nine categories, including information and rationale, assigning/discussing behavioral tasks, and so forth. In addition, for both PCT and drug conditions, raters recorded any verbalization that was inappropriate (e.g., off-target, alternative therapeutic techniques). Raters were also asked to determine the particular treatment condition and which of the three phases of treatment yielded the sample.

In all cases, raters correctly identified the treatment condition represented by the sample as well as the treatment phase from which the sample came. Across all conditions, there were only two instances of inappropriate material, both of which referred to nontargeted problem areas and not to the application of inappropriate treatment techniques. Thus, in both drug and PCT conditions, treatment was delivered as intended.

RESULTS

Attrition

Out of 69 initial subjects, 57 subjects completed the study, and 12 subjects dropped out. A higher rate of dropout was observed in the placebo group compared with the other three groups. One subject out of 17 (5.9%) dropped from the alprazolam group, 7 out of 18 (38.9%) from the placebo group, 3 out of 18 (16.7%) from the PCT group, and 1 out of 16 (6.3%) from the waiting-list group.

A chi-square analysis on these dropout frequencies was significant, $\chi^2(3, N = 69) = 8.75$, $P < 0.05$. Separate chi-squares on each pair of groups showed significant differences between the placebo and alprazolam groups, $\chi^2(1, N = 35) = 3.69$, $P < 0.05$; the placebo and PCT groups, $\chi^2(1, N = 36) = 3.01$, $P < 0.05$; and the placebo and waiting-list groups, $\chi^2(1, N = 34) = 3.45$, $P < 0.05$.

Subjects who dropped from the study were questioned about their reasons. Of the 7 subjects who dropped from the placebo treatment group, 3 reported they disliked the side effects of the study medication, and 3 developed intense panic attacks in the 1st week of treatment that the psychiatrist regarded as intolerable, causing him to drop them from the study (1 worked with dangerous equipment, 1 reported suicidal ideation, and 1 reported she felt unable to continue in her current state). The 7th subject reported she changed her mind about study participation and returned her first bottle unopened. Two of the 3 PCT dropouts decided they did not have the necessary time to devote to therapy. One who was unemployed when the study began started working and dropped out after 3 weeks, and a 2nd subject's duties increased, causing her to drop out after 5 weeks. A 3rd wished to resume medication and dropped out after 5 weeks. The waiting-list dropout reported insufficient time to complete the periodic measures and dropped after 8 weeks. Those who dropped

from the study were compared with study completers on major pretreatment variables. No major differences emerged on demographic, self-monitoring, medical, or clinical assessment variables related to panic disorder including Hamilton Anxiety and Depression scales. However, a few significant differences did appear in several tangential questionnaires not reported in this manuscript (see Klosko, 1987).

Since all placebo subjects dropped from the study before completion of 3 weeks of treatment, endpoint analyses were not conducted (e.g., as were conducted in the Ballenger et al., 1988, study). It is likely that the status of dropouts when they left the study is most adequately represented by their scores on pretreatment assessment measures. To be conservative, other dropouts were also assumed to be unimproved.

Pretreatment Characteristics of Treatment Groups

Analyses were conducted on the 57 subjects who completed treatment to describe pretreatment characteristics and to identify pretreatment differences that might have occurred among the four groups. As appropriate, analyses used were either chi-squares (or Fisher's exact tests) or one-way analyses of variance (ANOVAs) across treatment groups.

Demographic characteristics. Fifteen men (26%) and 42 women (74%) completed the study. Mean age was 37 years (SD = 11.04). Thirty-one subjects (54%) were married, 19 (33%) were single, 6 (11%) were divorced, and 1 (2%) was separated. One dropout from the placebo group was Black; all other subjects were White. Analyses across groups of all demographic characteristics were nonsignificant.

Clinical assessment measures. All clinical assessment measures were derived through administration of the ADIS-R. Table 1 displays some diagnostic characteristics including extent of agoraphobic avoidance. Analyses across groups on all diagnostic characteristics including number and type of additional diagnoses were nonsignificant.

Subjects endorsed a mean number of DSM-III-R panic symptoms of 9.7 (SD = 2.3). Mean intensity on 0–4 rating scales, where 0 equals *none* and 4 equals *very severe*, was 1.5 (SD = 0.5) for somatic symptoms and 1.8 (SD = 0.9) for cognitive symptoms. (Symptoms not endorsed were assigned an intensity of 0, accounting for relatively low severities.) Mean Hamilton Anxiety Rating Scale score was 17.8 (SD = 5.4); mean Hamilton Rating Scale for Depression score was 12.44 (SD = 6.3). Analyses across groups on all these clinical assessment measures were nonsignificant.

Medication use. Table 1 also displays prestudy medication use. (One should note that, in the PCT treatment group, one subject reported use of both benzodiazepines and beta blockers, and in the waiting-list group, 3 subjects reported use of more than one medication.) Chi-square analyses were conducted on frequencies of use of each medication and use of medication generally. Significant results were obtained for use of benzodiazepines, $\chi^2(3, N = 57) = 7.84, P < 0.05$, and use of medication generally, $\chi^2(3, N = 57) = 7.59, P < 0.05$. For use of benzodiazepines, separate chi-squares (or Fisher's exact tests) on each pair of groups, including the waiting-list versus the placebo groups, showed no significant differences; for use of medication generally, separate chi-squares (or Fisher's exact tests) showed significant differences between the PCT and waiting-list groups, $\chi^2(1, N = 30) = 5.17, P < 0.05$, and placebo and waiting-list groups, $\chi^2(1, N = 26) = 5.04, P < 0.05$. Results were nonsignificant for antidepressants, beta blockers, and antipsychotics.

Subjects from the three treatment groups (alprazolam, placebo, and PCT) were withdrawn from current medications as part of pretreatment medical procedures. They remained medication-free for approximately

TABLE 1. Pretreatment diagnostic characteristics and medication use of treatment groups

Variable	Alprazolam (n = 16)		Placebo (n = 11)		PCT (n = 15)		Waiting List (n = 15)		Total (N = 57)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Diagnosis										
Panic disorder, uncomplicated	5	31.3	3	27.3	2	13.3	2	13.3	12	21.1
Panic disorder, mild avoidance	9	56.3	7	63.6	13	86.7	11	73.3	40	70.2
Panic disorder, moderate to extensive avoidance	2	12.5	1	19.1	0	00.0	2	13.3	5	8.8
Global clinical severity ratings of panic disorder diagnoses										
Mean	5.38		5.36		5.00		5.47		5.30	
SD	0.885		0.674		0.845		0.990		0.865	
Medication use										
Benzodiazepines	11	68.8	4	36.4	6	40.0	12	80.0	33	57.9
Antidepressants	0	00.0	0	00.0	0	00.0	2	13.3	2	3.5
Beta blockers	0	00.0	0	00.0	1	6.7	2	13.3	3	5.3
Antipsychotics	0	00.0	0	00.0	0	00.0	0	00.0	0	00.0
Total medication use	11	68.8_{ab}	4	36.4_{a}	6	40.0_{a}	13	86.7_{b}	34	59.6

Note: PCT = panic control treatment. Groups with different subscripts are significantly different, $P < 0.05$.

1 week and were administered plasma benzodiazepine screens to ensure compliance with medication withdrawal before treatment began. Of the 42 subjects who were administered plasma benzodiazepine screens, no medication was detected in 37 (88.1%). Four subjects (9.5%) gave samples in which desmethyldiazepam was detected. Because this substance can remain in the blood longer than 1 week after discontinuation, these subjects were permitted to start treatment. One blood sample from a therapy subject was lost. However, this subject reported no medication use pretreatment, and her posttreatment sample was clean. Chi-square analyses of pretreatment samples were all nonsignificant.

Self-monitoring measures. In the 2-week period pretreatment, on the weekly record, subjects reported a mean number of panic attacks per week of 2.0 (SD = 1.9). Mean number of spontaneous attacks was 1.1 (SD = 1.4). Mean intensity of attacks, on a 0–8 scale on which 0 equals *none*, 4 equals *moderate*, and 8 equals *as much as one can imagine*, was 4.5 (SD = 2.2).

Subjects reported a mean of 1.9 (SD = 1.9) anxiety episodes in the 2-week pretreatment period. Mean intensity was 3.3 (SD = 2.3). One-way ANOVAS on frequency and intensity of panic attacks and anxiety episodes across groups were all nonsignificant.

POSTTREATMENT ASSESSMENT

General Approach

The strategy for identification of pretreatment differences among groups, with separate chi-squares or ANOVAS on each pretreatment measure, represented a liberal approach, and although a large number of tests were conducted, the alpha level remained at 0.05. Nevertheless, few pretreatment differences were uncovered.

In view of this pretreatment equivalence of groups, the general strategy for analyzing posttreatment data was administration of multivariate analyses of variance (MANOVAS) on posttreatment measures. In an effort to account for baseline (pretreatment) values, repeated-measures MANOVAs were also conducted on all analyses. Since the pattern of results was identical in each instance, we have chosen to present results of MANOVAs on posttreatment variables, because this approach provides the most straightforward identification of post hoc differences among pairs of means. Clinical assessment, medical assessment, self-monitoring, and psychophysiological measures were analyzed separately. Within each type of measure, variables were grouped thematically. Examples of the various themes included global panic disorder severity, panic, general anxiety, and depression. To explore further the nature of MANOVAS with statistically significant results, univariate ANOVAS were conducted upon each dependent variable included in the analysis. We performed post hoc comparisons among all pairs of means, using Duncan's Multiple Range Test (MRT; $P < 0.05$).

Dose

Alprazolam was increased rapidly to maximum average daily dose of 4.60 mg (SD = 1.82). Although every attempt was made to reach 6.0 mg, in some cases the clinical response was satisfactory at a lower dose; in others, side effects precluded higher dosage. Maximum average daily dose of placebo was somewhat higher at 5.08 (SD = 2.65).

Posttreatment Clinical Assessment Measures

Posttreatment clinical assessment measures were gathered through administration of a short form of the ADIS-R. The ADIS-R administrators were blind to group assignment.

Global clinical ratings. Clinical ratings of severity of panic disorder, assigned by ADIS

administrators before and after treatment, represent the most global study measure. Ratings were based on levels of psychological distress and interference in functioning produced as a function of panic disorder. The top of Table 2 presents posttreatment global clinical ratings.

A one-way ANOVA on posttreatment clinical ratings was significant, $F(3,53) = 4.12$, $P < 0.01$. Results of Duncan's MRT indicated that the alprazolam and PCT treatment groups were significantly more improved than the waiting-list group.

To conduct a test of endstate functioning, study completers were grouped according to whether they had obtained posttreatment global clinical ratings of clinical versus nonclinical severity as defined on the ADIS. They were grouped as subjects with low endstate functioning if they obtained ratings greater than or equal to 4 (clinical severity) or as subjects with high endstate functioning if they obtained ratings less than 4 (nonclinical severity). Approximately half of study completers obtained high endstate functioning. The next part of Table 2 displays the number and percentage of subjects with low and high endstate functioning. A chi-square analysis of these frequencies was significant, $\chi^2(3, N = 57) = 8.62$, $P < 0.05$. Separate chi-squares showed the PCT group was significantly different from the waiting-list group, $\chi^2(1, N = 30) = 6.56$, $P < 0.01$.

Since the placebo group had a disproportionate number of dropouts, it is reasonable to argue that analysis of endstate functioning that includes only study completers represents a distortion of results. Given the reasons and the rapidity (within the first 3 weeks) with which most subjects dropped from the study, it is likely that, at time of study withdrawal, dropouts maintained their pretreatment low endstate functioning status. The bottom of Table 2 presents subjects who obtained high versus low endstate functioning, with dropouts included. A chi-square analysis of these frequencies was significant, $\chi^2(3, N = 69) = 7.86$, $P < 0.05$. Separate chi-squares showed once again that the PCT group was significantly different from the waiting-list group, $\chi^2(1, N = 34) = 4.65$, $P < 0.05$.

Measures of general anxiety. Univariate ANOVA on Hamilton Anxiety Rating Scale scores was significant, $F(3,53) = 3.19$, $P < 0.05$. Results of Duncan's MRT showed that the PCT group was significantly more improved than the waiting-list group. Means

TABLE 2. Posttreatment clinical assessment measures of treatment groups: global clinical ratings

Variable	Alprazolam	Placebo	PCT	Waiting List	Total
Sample size (n)					
Completers	16	11	15	15	57
Total	17	18	18	16	69
Disorder severity[a]					
Mean	3.56_a	3.55_{ab}	2.73_a	4.80_b	3.67
SD	1.90	1.51	1.53	1.47	1.76
Endstate nonclinical severity[b]					
Completers					
n	8	5	11	3	27
%	50.0	45.5	73.3_a	20.0_b	47.4
Total					
n	8	5	11	3	27
%	47.1_{ab}	27.8_{ab}	61.1_a	18.8_b	39.1

Note: PCT = panic control treatment. Subscripts indicate that values differed significantly at $P < 0.05$.
[a]Panic disorder severity was assessed using the Anxiety Disorder Interview Schedule–Revised (ADIS-R).
[b]Endstate functioning was assessed on the ADIS-R by assigning ratings of clinical or nonclinical severity.

and standard deviations of pretreatment and posttreatment scores on the Hamilton Anxiety Rating Scale were as follows: alprazolam mean, pretreatment = 18.75 (SD = 5.74), posttreatment = 13.68 (SD = 7.02); placebo mean, pretreatment = 17.36 (SD = 5.59), posttreatment = 13.36 (SD = 5.63); PCT mean, pretreatment = 16.93 (SD = 5.43), posttreatment = 9.80 (SD = 5.31); and waiting-list mean, pretreatment = 18.07 (SD = 5.22), posttreatment = 16.27 (SD = 4.71).

Posttreatment Medication Use Measures

As noted, alprazolam and placebo subjects who were able to withdraw completely from medication did so; subjects who experienced difficulty were permitted to resume stable dosage, at or near levels they received during the study, before posttreatment assessment. There were several justifications for this method. It soon became apparent that many subjects were unwilling to withdraw from their study medication. Rather than continue tapering indefinitely for these subjects, tapering was stopped. It seemed methodologically unsound to conduct posttreatment assessments on medication subjects while they were in states of withdrawal; hence, subjects who could not withdraw were stabilized once again before undergoing assessments. In fact, only 1 out of 16 subjects withdrew completely from alprazolam. The remaining 15 were quickly stabilized at or near their study dosage level. In contrast, 2 subjects out of 11 in the placebo group were "unable to withdraw" and were stabilized at study dosage levels.

Subjects were not pressured to withdraw from medication. Subjects who experienced even mild difficulty were permitted to resume their study dosage levels very quickly. No subject exhibited extreme withdrawal symptoms. Thus, it is unlikely that attempts to taper alprazolam exerted any negative effect upon their scores on posttreatment assessment measures. This assertion is supported by analyses of the panic data preceding attempts to withdraw subjects from their study medication compared with posttreatment. Panic measures were taken from the last available weekly record before patients were instructed to begin taper withdrawal. Subjects in the alprazolam group had a mean number of panic attacks of 0.94 (SD = 1.61) and a mean intensity of panic of 2.06 (SD = 2.91). These figures are slightly higher than the mean number and intensity of panics for alprazolam subjects posttreatment (see Table 3). Approximately 63% of alprazolam subjects were panic-free before taper withdrawal. Therefore, before taper withdrawal, slightly fewer alprazolam subjects were experiencing panic attacks in comparison with posttreatment, but those subjects who were still experiencing panic were having more frequent and severe attacks in comparison with posttreatment.

Two procedures were used to determine posttreatment medication use: self-report during posttreatment ADIS administration and collection of plasma benzodiazepine screens for tests of medication content. The latter procedure applied to subjects in the alprazolam, placebo, and PCT treatment groups only. Posttreatment, 29 subjects reported medication use. The reports were consistent with protocol with the exception of 2 placebo subjects who reported taking benzodiazepines despite plasma benzodiazepine screens that confirmed they were on placebo. These were the 2 subjects who also were unable to withdraw from placebo and were restabilized and thus were the only 2 placebo subjects still taking drugs.

Of the 42 subjects who completed one of the three active treatments, 28 had posttreatment plasma benzodiazepine screens. Blood tests were missing or not available for 14 subjects. No deviations from protocol were revealed through plasma benzodiazepine screens.

Psychiatrist ratings of medication effectiveness. As part of posttreatment assessment, the psy-

chiatrist rated the effectiveness of the study medication for each medication group subject through use of the poststudy termination record. While remaining blind to group assignment, the psychiatrist compared the study medication with "usual drug treatment of this disorder." Ratings ranged from *noneffective* (1) to *much more effective* (6). The mean rating the psychiatrist assigned to subjects in the alprazolam group was 4.13 (SD = 0.72); the mean rating he assigned to subjects in the placebo group was 2.73 (SD = 1.10). A one-way ANOVA on ratings of medication effectiveness was significant, $F(1,25) = 15.97$, $P < 0.001$.

Panic ratings. A MANOVA was conducted on posttreatment panic ratings from the ADIS-R, with number of symptoms endorsed, mean intensity of somatic symptoms, and mean intensity of cognitive symptoms as dependent measures. It was significant, Pillais $F(9,159) = 2.14$, $P < 0.05$. Table 3 presents these results.

A univariate ANOVA on number of symptoms endorsed was significant, $F(3,53) = 2.79$, $P < 0.05$. Results of Duncan's MRT showed that the PCT group was significantly more improved than the waiting-list group. A univariate ANOVA on mean severity of somatic symptoms was significant, $F(3,53) = 3.69$, $P < 0.05$. Results of Duncan's MRT showed that the PCT group was significantly more improved than the alprazolam and waiting-list groups. A univariate ANOVA on mean severity of cognitive symptoms was significant, $F(3,53) = 3.69$, $P < 0.05$. Duncan's MRT showed that the PCT group was significantly more improved than the waiting-list group. For all symptoms, a univariate ANOVA was significant, $F(3,53) = 3.79$, $P < 0.05$. Results of Duncan's MRT showed that the PCT group was significantly more improved than the alprazolam and waiting-list groups.

Since voluntary hyperventilation and breathing retraining to control symptoms of hyperventilation were important components of cognitive-behavioral therapy, the panic symptom dyspnea was explored separately. There were no significant differences for severity of dyspnea among groups pretreatment, but at posttreatment a univariate ANOVA was significant, $F(3,53) = 3.74$, $P < 0.05$. Duncan's MRT scores indicated that the PCT group was significantly more improved than the alprazolam and waiting-list groups.

Self-Monitoring Measures

Measures of panic attacks. The middle of Table 3 displays posttreatment weekly record measures of panic frequency and intensity. Univariate ANOVAs were significant for posttreatment panic frequency, $F(3,53) = 2.78$, $P < 0.05$, and intensity, $F(3,53) = 3.81$, $P < 0.05$. For both, Duncan's MRT showed that the alprazolam and PCT groups were significantly more improved than the waiting-list group. A MANOVA, with number of spontaneous and number of cued panic attacks as dependent measures, was nonsignificant.

Thirty subjects recorded zero panic attacks in the 2-week period posttreatment. The bottom of Table 3 displays the number of subjects who recorded zero panic attacks versus the number who recorded one or more panic attacks. A chi-square analysis of these relative frequencies was significant, $\chi^2(3, N = 57) = 5.21$, $P < 0.05$. Separate chi-squares showed that the PCT group was significantly different from the placebo, $\chi^2(1, N = 26) = 5.05$, $P < 0.05$, and waiting-list, $\chi^2(1, N = 30) = 6.80$, $P < 0.01$, groups.

The number of subjects who recorded zero (versus one or more) spontaneous attacks and the number who recorded zero (versus one or more) cued attacks are also presented. Chi-square analyses of these relative frequencies were nonsignificant.

DISCUSSION

Results of this study confirm uncontrolled clinical trials suggesting the existence of an effective behavioral treatment for panic disorder. Over 85% of the patients who received behavior therapy were panic-free for a 2-week

period at the end of treatment. This was significantly better than results observed in placebo and waiting-list conditions, although not significantly better than the alprazolam condition. The alprazolam group did not differ significantly from either behavior therapy or placebo. However, the study psychiatrist's blind ratings of medication effectiveness at posttreatment did pick up drug-placebo differences. Presumably he was reacting to a number of cues available during weekly visits in comparison with independent raters who only saw the subjects once at posttest. These cues, of course, also may have confounded the blind ratings.

Behavior therapy surpassed alprazolam on reductions in intensity of somatic panic attack symptoms generally and the specific panic symptom dyspnea. This latter finding might reflect the emphasis on breathing training in the therapy group. Nevertheless, the finding is somewhat surprising because cognitive-behavioral approaches are thought to impact on panic and anxiety by affecting cognitive rather than somatic symptoms. In this study, however, both cognitive and so-

TABLE 3. Posttreatment clinical and self-monitoring measures of panic and panic frequency in each group

Measure	Alprazolam (n = 16)	Placebo (n = 11)	PCT (n = 15)	Waiting List (n = 15)	Total (N = 57)
			Clinical ratings		
Number of symptoms endorsed					
Mean	6.06_{ab}	6.90_{ab}	4.40_{a}	7.64_{b}	6.20
SD	4.28	3.11	2.82	2.02	3.34
Intensity of somatic symptoms					
Mean	1.03_{a}	0.89_{ab}	0.56_{b}	1.15_{a}	0.91
SD	0.65	0.46	0.52	0.39	0.55
Intensity of cognitive symptoms					
Mean	0.67_{ab}	0.85_{ab}	0.47_{a}	1.29_{b}	0.91
SD	1.04	0.50	0.44	1.03	0.55
			Self-monitoring of panic attacks		
Frequency per week: total					
Mean	0.51_{a}	0.56_{ab}	0.20_{a}	1.72_{b}	0.76
SD	0.81	0.85	0.65	2.73	1.62
Frequency per week: spontaneous					
Mean	0.24	0.32	0.03	0.65	0.31
SD	0.63	0.60	0.13	0.96	0.68
Intensity					
Mean	1.66_{a}	1.78_{ab}	0.71_{a}	3.53_{b}	1.92
SD	2.08	2.04	1.99	3.01	2.50
			Frequency of panic attacks		
Experienced zero panic attacks					
n	8	4	13	5	30
%	50.0_{ab}	36.4_{a}	86.7_{b}	33.3_{a}	52.6
Experienced zero spontaneous attacks					
n	10	6	13	6	35
%	62.5	54.5	86.7	40.0	61.4
Experienced zero cued (situational) attacks					
n	9	7	14	10	40
%	56.3	63.6	93.3	66.7	70.2

Note: PCT = panic control treatment. Groups with different subscripts are significantly different at $P < 0.05$.

matic aspects were reduced.

Differential attrition across groups was noteworthy. Significantly more subjects dropped from the placebo group than from the alprazolam, PCT, or waiting-list groups, with more subjects dropping from the placebo group than from the other three groups combined. The high rate of dropouts from this group replicates a finding in the Upjohn multicenter study (Ballenger et al., 1988), but the pattern is different. In Ballenger et al., most placebo subjects dropped out between 3 and 8 weeks. In our study, all subjects dropped out before 3 weeks. This may reflect, in part, the conservative clinical strategy of the study psychiatrist who discontinued (dropped) subjects from the study if they were having difficulty. In any case, if one considers only completers, then 45% of placebo completers achieved high endstate functioning posttreatment; but if one includes dropouts, only 28% of placebo subjects achieved high endstate functioning. As in the Ballenger et al. study, the true estimate of placebo response (and therefore the drug-placebo differential) probably lies somewhere between these two percentages.

Subjects assigned to the waiting-list condition were taking significantly more medication pretreatment and were not required to withdraw from medications. Although pretreatment severity ratings between waiting-list and other groups were not significantly different, presumably these subjects would have fared worse if they had been required to withdraw from medications. Thus, comparisons between waiting-list subjects and other groups tend to be conservative.

An additional caution we have alluded to concerns the fact that posttreatment measures in the alprazolam group were taken after attempts to withdraw these clients from alprazolam. When this did not prove feasible, subjects were quickly restabilized on study dosages, and data would suggest that withdrawal symptoms did not adversely influence posttreatment measures. Nevertheless, the possibility still exists that this adverse influence occurred in some patients. In fact, evidence now suggests that relapse is common if withdrawal from alprazolam (or other benzodiazepines) is successfully completed and that discontinuation effects in themselves are a major obstacle to therapeutic success with relapse rates ranging from 80–95% (e.g., Fyer et al., 1987; Pecknold, Swinson, Kuch, and Lewis, 1988).

Finally, our study provides only a preliminary statement of the relative effectiveness of two very different treatments for the debilitating condition of panic disorder. As illustrated in Barlow and Cerny (1988), measures of percentage free of panic attacks as the central measure of outcome may prove to be an overly optimistic gauge of therapeutic success. Panic disorder is an anxiety disorder, and the fundamental difficulty may not be the occurrence of panic attacks, which occur in a large percentage of the population (e.g., Norton, Dorward, and Cox, 1986), but may rather be severe anxiety over the possibility of having another attack. Generalized anxiety as measured by the Hamilton Anxiety Rating Scale dropped approximately 10 points from relatively severe levels across all treatment groups in both the Ballenger et al. (1988) study and in our study, suggesting that these clients continue to present with substantial anxiety. In fact, in 50% or more of these clients there is considerable room for improvement (e.g., see Barlow and Cerny, 1988). Future studies must ascertain not only the mechanisms of action of these various treatments but also the ways to make them more powerful, more efficient, and more permanent, either singly or in combination.

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