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Long-Term Effectiveness of Combined Alprazolam and Cognitive-Behavioral Therapies in Panic Disorder

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Running Head: LONG-TERM EFFECTIVENESS OF COMBINED THERAPIES

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Abstract

Benzodiazepines, particularly alprazolam, have been shown to be effective in the acute treatment of panic disorder. Difficult withdrawal and high relapse rates after successful discontinuation continue to be problems with this class of medication. Recent studies instituting cognitive-behavioral therapy as a treatment supplement to alprazolam taper, have shown promising results out to one year follow-up. The present study investigated whether that combined treatment results in long-term improvement. Patients were stabilized on alprazolam and randomly assigned to either an alprazolam-only group or the same condition with twelve weeks of concurrent cognitive-behavioral therapy. Twenty patients completed the study. During the 24-48-month post-treatment evaluation, nearly 70% of those receiving combined treatment had remained off drug or other supportive panic disorder therapy compared to the 30% for the alprazolam-only group. From scores on self-report and clinician-rated measures, the combined treatment appeared to have been effective in producing a high end-state functioning as well as in facilitating alprazolam discontinuation.

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Long-term Effectiveness of Combined Alprazolam and Cognitive-Behavioral Therapies in Panic Disorder

Panic disorder with agoraphobia (PDA), which has a prevalence of one to two percent in the general population, typically begins in a patient's mid-twenties and occurs twice as frequently in women as in men (24). Like all anxiety disorders, it has the trademark symptoms of anxiety and avoidance. However, PDA can be distinguished from other anxiety disorders, especially phobias, by the characteristic "spontaneous" panic attacks, which are not reliably and exclusively elicited by some specific object or situation. Consequently, panic patients can experience the attacks with no forewarning and no predictive stimulus (14). During the attacks patients may experience any of the following symptoms: shortness of breath, dizziness, tachycardia, trembling or shaking, sweating, choking, nausea, hot flashes or chills, feelings of numbness or tingling, depersonalization/ derealization, a fear of dying, or a fear of going crazy without the ability to control one's actions. To meet the diagnostic criteria for PDA, a patient must experience at least four of these symptoms during a panic attack and begin avoiding situations for fear of their recurrence (2).

In agoraphobia, patients tend to modify their activities in order to avoid situations in which escape might be difficult or impossible, help may not be available, or embarrassment might result if another panic attack occurred. This modification, termed "fear of fear", is often targeted in the course of treatment (15). Certainly panic attacks

that result from cued and uncued stimuli and the anticipatory anxiety from one attack to the next can greatly affect the normal functioning of an individual.

The two primary treatment modalities for PDA are pharmacologic and nonpharmacologic. Benzodiazepines, the only medication for PDA approved by the Food and Drug Administration, have several advantages: their antipanic properties are evident almost immediately (3); their effectiveness is maintained over "as needed", short, and long-term dosage schedules; they have no long-term adverse effects on any organs; ingested overdoses are virtually non-lethal (14). Gitlin (1990) designates the benzodiazepines as the safest of the psychotropic medications presently in use.

Part of benzodiazepine's efficacy may be a function of its mode of action. Tallman, Thomas, and Gallagher (1978) showed that the benzodiazepines enhance the widespread inhibitory activity of gamma-aminobutyric acid (GABA) in the brain. Moreover, the juxtaposition of the GABA and benzodiazepine receptors on the same receptor complex and their necessary joint stimulation is responsible for the influx of extracellular free chloride ions and the subsequent inhibited firing of those neurons (14). A high concentration of benzodiazepine-GABA receptor complexes is found in the locus ceruleus, the primary noradrenergic nucleus, hyperactivity of which has been considered to be centrally involved in the etiology of PDA (for review, see Gorman et al, 1989). By reducing the norepinephrine activity in the overstimulated projections of the locus cereleus with

benzodiazepines, an overall attenuation of symptoms, namely a suppression of the spontaneous panic attacks, can be achieved (17).

Alprazolam, a high potency benzodiazepine, has been shown in large trials to be a particularly efficacious treatment modality for PDA (28, 3). Despite the clear benefits of alprazolam, it also has drawbacks. Alprazolam induces true physiological dependence and shows a distinct withdrawal syndrome when discontinued (23). Withdrawal symptoms can include agitation, forgetfulness, tremor, insomnia, nausea, sweating, and tachycardia. There have been only rare instances where benzodiazepine discontinuation has elicited paranoia, severe depression, delerium, or grand mal seizures (14). In addition to the dependence and withdrawal complications, alprazolam therapy has been characterized by high relapse rates (10).

Given its widespread use in the clinical treatment of anxiety disorders, mental health professionals have been proposing several strategies to ameliorate discontinuation symptoms that complicate alprazolam taper. One such method of facilitating withdrawal involves the temporary addiction to other medications such as carbamazepine, imipramine, or buspirone during taper (26). A study by Ries, Roy-Byrne, Ward, Neppe, & Cullison (1989) showed that patients given carbamazepine before rapid discontinuation of benzodiazepines tolerated the taper well with no one reporting significant withdrawal symptoms or side effects. Another suggested treatment strategy consists of modifying taper by changing patients

from an intermediate-acting benzodiazepine (alprazolam) to a longer-acting agent (clonazepam) before the initiation of discontinuation (14,1). While these studies show that medication strategies are helpful when taper is rapid, a slow flexible taper is sufficient to assist discontinuation; however, relapse after discontinuation remains a problem (30, 19).

The major non-pharmacological approach to PDA involves cognitive-behavioral therapy (CBT). A primary target of CBT is to reduce the catastrophic misinterpretations of panic symptoms such as cardiac arrhythmia, breathlessness, and lightheadedness, which may be perceived as heart attack precursors instead of the somatic sensations in normal anxiety responses (9).

Cognitive-behavioral therapy has been shown to have high acute treatment success rates with low relapse rates. For example, Craske, Brown, and Barlow (1991) assessed 41 panic disorder patients with mild or no agoraphobic avoidance who had participated in either progressive muscle relaxation, interoceptive exposure therapy and cognitive restructuring, or a combination of both conditions. Of the patients receiving cognitive restructuring, 81% remained panic-free at two-year follow-up. Similarly, a study examining the treatment of agoraphobia at two years demonstrated that agoraphobics undergoing CBT maintained an improved end-state functioning over 24 months when a spouse was involved with therapy (6).

CBT formulations suggest that the withdrawal symptoms experienced by patients during benzodiazepine taper may be related to the difficulty in discontinuing their medications, in light of PDA patients' heightened anxiety and concern about bodily sensations (e.g. Otto et al., 1992). Several trials integrating CBT methods into alprazolam taper have produced promising results. For example, Otto et al. (1993) assessed the efficacy of a cognitive-behavioral program for 33 patients with PDA who were discontinuing treatment with high potency benzodiazepines. Panic patients randomly assigned to drug condition or drug condition with ten weeks of concurrently taught CBT were tapered off of alprazolam or clonazepam (mean subtherapeutic dose=1.3 mg/day and 1.5 mg/day respectively). Successful discontinuation of benzodiazepine treatment was significantly lower for those receiving slow taper alone (25%) than for those who underwent cognitive-behavioral restructuring during taper (76%); 77% of the latter remained free of benzodiazepines at three-month follow-up. In a similar follow-up study, Bruce et al. (1994) reported that panic disorder patients who received combined alprazolam/CBT experienced fewer symptoms at three months and were overall better responders to alprazolam discontinuation.

Spiegel, Bruce, Gregg, & Nuzzarello (1994) also assessed patients (N=21) who were made panic-free with alprazolam (mean dose=2.2 mg/day) and then assigned to either slow, flexible drug taper or drug taper with 12 weeks of CBT. At the completion of the study, there were no significant differences between the groups

concerning the rate of alprazolam discontinuation; however, at six month follow-up, 50% of the alprazolam-only group (N=10) and none of the combined alprazolam/CBT group (N=10) relapsed and had to reinstate pharmacotherapy. This result suggests that the drug taper protocol was sufficient to increase the discontinuation rate, but the CBT prevented relapse. Another long-term follow-up at one year showed 76% of the patients were medication-free and 85% were panic-free after a CBT model was employed during drug taper (18).

Although these results suggest that CBT can help patients successfully discontinue alprazolam and maintain gains through six month to one-year evaluations, treatments combining psychotherapy and benzodiazepines are not always beneficial. As was shown by Marks et al. (1993) in one large trial, implementing anxiety management techniques and in vivo exposure therapy as treatment supplements did not produce encouraging results. In that study, there were no significant differences in relapse rates between the CBT-only group (56%) and those receiving CBT after drug discontinuation (52%). Consequently, it remains controversial if combined therapy will be as viable a treatment modality as CBT-only over long-term assessments.

To our knowledge, no studies have investigated the effects of combined CBT and alprazolam at long-term follow-up. The purpose of the present study was to evaluate the clinical functioning of combined alprazolam and CBT at two- to four-year assessment and to see if efficacy is maintained. We hypothesized that individuals

receiving CBT during taper would be more successful in remaining drug abstinent compared to patients who taper off alprazolam without concurrently taught cognitive-behavioral therapy. We also predicted that members of the combined group would maintain their therapeutic gains through long-term follow-up.

Method

Participants

Participants were recruited from the patient population at the University of Illinois College of Medicine at Peoria who met the DSM-III-R diagnostic criteria for panic disorder with agoraphobia of at least six months' duration. Assessments were made with the Anxiety Disorders Interview Schedule-Revised (ADIS-R) (13) and the Structured Clinical Interview for DSM-III-R-Personality Disorders (SCID-II, Version 1.0) (31). Patients were excluded from the study if they met DSM-III-R criteria for an organic mental syndrome, major mood disorder, or obsessive-compulsive disorder; had been treated previously with cognitive-behavioral therapy for panic disorder; were presently in psychotherapy, or were taking other centrally-acting medications besides alprazolam. Similarly, if patients presented with mental illness, pregnancy, lactation, or a history of psychosis or drug dependency within the past year, they were not included. To be considered for the study, patients had to have alprazolam as their only centrally-acting medication in daily dosages between 1 and 10 mg. They also had to be free of spontaneous panic

attacks for at least four weeks. For those individuals who met all criteria except these, a washout period followed by alprazolam stabilization was instituted before their enrollment into the program.

Twenty-four participants were included, four men and 20 women (mean age=38 years, average duration of PDA=12 years). At screening, of the 15 who were on anxiolytics, 12 were taking benzodiazepines, and one patient each was taking buspirone, propranolol, and desipramine.

All participants presented with symptoms at screening despite being on pharmacotherapy. Patients suffered from a weekly average of 1.6 panic attacks and 4.6 limited symptom attacks before alprazolam stabilization. Over 70% of the group complained of nocturnal panic episodes. Following DSM-III-R criteria, 19% of the patients were rated as having mild panic, whereas 52% and 29% of the patients met the guidelines for moderate and severe panic, respectively. Agoraphobic avoidance was rated as mild for eight, moderate for 12, and severe for one of the patients. Forty-eight percent of the group had one additional anxiety disorder, while nine percent met criteria for two or three. Specifically, the comorbid diagnoses included general anxiety disorder (33%), simple phobia (29%), and social phobia (9%).

Each person was stabilized on alprazolam before enrollment (mean duration=6.3 weeks, including four weeks following the final stabilized dosage). The mean alprazolam dose was 2.2 mg/day.

Treatments

After alprazolam stabilization and enrollment, participants were randomly assigned to either an alprazolam and taper with supportive medical management (N=10), or the identical treatment with twelve weeks of concurrently taught cognitive-behavioral therapy (N=14). So as to minimize patients' bias against the drug only condition, all participants were told that the study was comparing two methods of alprazolam administration and discontinuation. Each person consented to random assignment and the institutional review board approved of the handling of human participants.

Treatment integrity was monitored through random assessments of 30% of the cognitive-behavioral and supportive therapy audiotapings. Treatment adherence scales by Barlow and Craske were used to check the cognitive-behavioral sessions. To ensure patient compliance with the pharmacotherapeutic protocol, weekly pill counts, patient diaries of alprazolam use, and serum benzodiazepine levels at two, six, and 15 weeks post-taper were employed.

Pharmacotherapy. Alprazolam maintenance and taper consisted of two phases which were identical for both groups of patients. The stable-dose maintenance phase (mean duration=11.0 weeks) reflected that time during which the patient was maintained on the pre-enrollment dose; the taper phase (mean duration for those who completed taper=6.5 weeks) included a decrease in alprazolam dosages in open label fashion every seven days until either

discontinuation was complete or the patient refused to decrease the dose any further. Depending on the initial maintenance dose, participants' daily alprazolam intake was tapered down to 2 mg, then to 1.5, 1.0, 0.75, 0.5, 0.375, 0.25, 0.125, and finally 0 mg.

Supportive medical management for patients was provided weekly to both groups by a psychiatrist during the stable-dose and taper phases of alprazolam withdrawal. Follow-up visits consisted of biweekly consultations for three months and then a brief final contact after six months. Extensive precautions were taken to ensure that the psychiatrist was blind to the treatment conditions.

Cognitive-behavioral therapy. Patients in this group differed from their drug-only counterparts solely by the twelve weeks of CBT that was administered concurrently through alprazolam taper. During these sessions, participants individually received the CBT in accordance to manuals developed by Barlow and Craske (1989). Treatment included education about panic disorder, diaphragmatic breathing training, cognitive restructuring, and interoceptive exposure. The latter was initiated at the beginning of drug taper whereas the former three aspects of therapy were introduced during the stable-dose phase. With this [illegible] cognitive-behavioral session, after which time, the patient had no contact with the intervening therapists.

Measures

Alprazolam discontinuation. The primary outcome measure was the number of individuals who completed all steps of taper in the

time allotted by the treatment protocol and who did not relapse back on to pharmacotherapy or enroll in alternative PDA treatment throughout the two- to four-year follow-up.

Clinician-rated and self-report assessments were done at baseline, three-month post-taper, and two- to four-year post-taper follow-up. Using the Sheehan Panic and Anticipatory Anxiety Scale, the occurrence of panic attacks or limited symptom attacks during the preceding two weeks, and the intensity of anticipatory anxiety episodes were evaluated (29). Patients' fear of situations was assessed on the Anxiety Disorders Interview Schedule-Fear (13), and their level of agoraphobic avoidance when alone was rated by using the Mobility Inventory for Agoraphobia (8). Cognitive features of PDA were assessed using the Anxiety Sensitivity Index (25), the Agoraphobic Cognitions Questionnaire (7), and the Emotional Control Questionnaire (Rapee, Craske, and Barlow; presented at the 1989 annual meeting of the Association for Advancement of Behavioral Therapy). Depression was measured with the Beck Depression Inventory (4) (see appendices A-G).

Results

Participants

One participant in the combined alprazolam and CBT group did not complete taper due to the discovery that she had been started on a centrally-acting drug regimen other than alprazolam for a medical

condition not related to anxiety. Three patients (two in the drug-only group and one in the combined group) failed to complete all steps of taper. Among the remaining 20 individuals, 16 managed to complete taper with the standard weekly dose reductions, three accomplished taper with one extra week required, and one needed an additional three weeks.

Measures

Two types of data analysis were performed: a survival analysis to evaluate discontinuation success between treatment groups and repeated measures analyses of variance (ANOVAs) to assess the efficacy of combined therapy between assessment periods.

Discontinuation Success. Figure 1 shows the percentage of patients who achieved and maintained drug and other PDA treatment abstinence through follow-up. Success rates at post-taper were high for both alprazolam-only (80%) and combined therapy groups (92%). At six-month follow-up, while 92% of the combined group continued to remain intervention-free, 60% of their drug-only counterparts had resumed medication. Those who relapsed cited increased panic and limited symptom relief attacks as the reasons for reinstating drug therapy. Assessments at 24-48 months post-taper showed that discontinuation success rates had fallen to 30% and 69.2% for the alprazolam and alprazolam+CBT groups. A survival analysis indicated that discontinuation rates before taper, post-taper, and at 24-48-month follow-up were significantly

different between the two groups (Lee-Desu statistic=10.539, df=1, $p<0.005$).

Repeated Measures ANOVAs. Differences between baseline, 3-month post-taper, and 2- to 4-year follow-up scores on clinician-rated and self-report measures in the combined group were compared using repeated measures ANOVAs. Omnibus tests that were significant, were followed up with planned comparisons using Fisher's two-tailed t-tests. Results from those t-tests are graphically represented in Figures 2-8. Figure 2 shows that scores on the Anxiety Disorders Interview Schedule-Fear differed significantly from baseline to three-month follow-up ($t=3.51$, $df=12$, $p<0.005$), three-month to 24-48-month follow-up ($t=9.96$, $df=11$, $p<0.001$), and from baseline to 24-48-month follow-up ($t=12.21$, $df=12$, $p<0.001$). Mean scores on the Mobility Inventory of Agoraphobia when Alone indicate significance levels from baseline to 3-month ($t=4.43$, $df=12$, $p<0.005$) and baseline to long-term follow-up ($t=4.58$, $df=12$, $p<0.001$).

Similar findings between baseline and 3-month and baseline to 2 to 4 year follow-up were evinced on the other evaluative tests (Figures 4-8). Scores on the Anticipatory Anxiety Scale were significant over the measurement periods ($t=2.73$, $df=12$, $p<0.05$) and ($t=2.90$, $df=11$, $p<0.05$) respectively as did the means from the Beck Depression Inventory ($t=2.15$, $df=12$) and ($t=2.77$, $df=11$) respectively. The Anxiety Sensitivity Inventory also was effective in detecting changes in patient functioning as was seen by the

significant decrease in scores from baseline to 3 months (t=3.46, df=12, p<0.01) and from baseline to 24-48 months (t=3.16, df=11, p<0.01)]. Scores on the Agoraphobic Cognitions Questionnaire reflected a similar decrease (t=2.55, df=12, p<0.05) and (t=3.80, df=11, p<0.005). Means on the Emotional Control Questionnaire were also significant from baseline to both 3-month (t=-2.79, df=12, p<0.05) and 24-48-month follow-up (t=-2.87, df=11, p<0.05).

Discussion

This paper presents data from patients with PDA who discontinued stable therapeutic doses of alprazolam with and without concurrent CBT. Spiegel et al. (1994) demonstrated that at six month post-taper, those individuals receiving the additional psychotherapy were significantly better than their alprazolam-only counterparts by remaining drug abstinent and panic-free.

The results reported here show that the high successful discontinuation rates seen in the combined group were persistent over two to four years. Nearly 70% of those participants did not need to return to medication and other treatment interventions. Suggesting that the significant difference between groups at long-term follow-up is necessarily attributable to the CBT, however, is specious, given that no CBT-only group was assessed at the same evaluation points. Studies examining the long-term effectiveness of CBT-only, though, have elucidated clearly the benefits of this

treatment modality with approximately 80% of patients maintaining therapeutic gains (6, 12).

Improvement evident on self-report and clinician-rated measures shows that the success of the alprazolam plus CBT participants to discontinue medication was not due to stoic endurance of symptoms, stubborn refusal to reinstate medication, or greater avoidance of panic-precipitating situations. Significant improvement was seen on most dimensions of PDA, including panic attack number, fear of situations, actual avoidance of situations, anticipatory anxiety, depression, fear of physiological sensations, catastrophic thinking, and locus of control, indicating that end-state functioning was high at two to four-year follow-up. Not only did mean scores remain low as in the anticipatory anxiety scale and the number of panic attacks (zero at baseline, 3-month, and 24-48-month post-taper), but scores showed a general decrease suggesting continued improvement from baseline to post-taper which maintained through follow-up. Scores on the Emotional Control Questionnaire increased over the course of the study which was reflective of patients' conception that emotions were more within their control. Patients were considerably less anxious and depressed, they reported less fear, and their avoidance of situations had decreased significantly. This A+CBT protocol facilitated alprazolam discontinuation and was responsible for clinical changes reflected in high end-state functioning at long-term follow-up.

Several cautions must be employed in interpreting these results, however. For one, although the participant sample was representative of larger N studies of PDA on many features, generalization of the findings should be guarded due to the small sample size. With 23 patients, the power of our statistics is less than optimal. Replication is necessary. Also, our results suggest that combined treatment is effective over the long-term, but without a proper control group, we cannot ascertain what elements of CBT+alprazolam accounted for the change in patient functioning from baseline to follow-up evaluation.

Despite these problems, these data are intriguing and deserve careful consideration. This treatment protocol, which gives PDA patients prompt relief from symptoms and the cognitive-behavioral change to maintain those gains through long-term follow-up, gives mental health professionals an additional treatment option. Combined therapy has been shown to be beneficial at three-month follow-up (5, 21), six-month follow-up (30), and at one-year evaluation (18). Our results provide the long-term (2- to 4-year) data necessary to ensure practitioners that implementing this particular method of integrating CBT and drug taper will produce lasting effects.

Future directions could focus on elucidating the mechanism of action by which integrated therapy has its effects. Other studies could also directly compare efficacies of CBT alone. Combined therapy appears to warrant further research.

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Appendix A

STRUCTURED INTERVIEW FOR SHEEHAN PANIC AND ANTICIPATORY ANXIETY SCALE (Revised for Study)

Subject Name _____ ID _____

Interviewer _____ Date _____

Now I would like to ask you about any panic attacks you may have experienced during the past week. By "panic attack" I mean specifically an episode or spell during which you suddenly felt frightened or extremely uncomfortable and had at least four of the symptoms on the list I will give you in a moment. By "suddenly" I mean that the symptoms reached their maximum intensity within 10 minutes from when you first noticed they were there or were getting worse. It is important that you are clear about how I am defining a panic attack. Are you clear about that? Do you have any questions?

(Rater: Answer any questions before proceeding)

Now please read carefully through the symptoms on this list, noting any you experienced during the past week that came on suddenly along with a feeling of fear or extreme discomfort. Take your time, and let me know when you are finished.

(Rater: Hand patient Symptom List and wait for signal).

A. PANIC ATTACKS:

O.K., now, during the past week, how many episodes in all have you had when you suddenly felt frightened or extremely uncomfortable and experienced at least four of the symptoms on the list? (I will ask you later about episodes when you had fewer than 4 symptoms.)

(Rater: Verify that all of the episodes reported involved at least four symptoms on the list and reached a peak within 10 minutes. Record Number/Week in blank at left.)

TPN_____

1. SITUATIONAL:

Now of those (insert number) attacks, how many occurred when you were in or just about to go into a place or situation that, in your experience, is likely to bring on an attack?

SPN_____ (Number/Week)

SPD_____ associated with those situations) last? **(Duration-minutes)**

On a scale of 1 to 10, with 1 being the least and 10 being the most anxious or uncomfortable you can imagine, how bad were most of those attacks? (Intensity -Score "0" if subject had

SPI_____ no attacks)

2. UNEXPECTED:

So then of the (total number from A) panic attacks you experienced during the past week, (number from A.1) occurred when you were in or about to go into a place or situation that, in your experience, is likely to bring on an attack, and all the others occurred when you were not in or about to go into such a place or situation? Is that correct?

(Rater: If no, clarify and revise answers to A.1 as needed. If yes, proceed).

That would be a total of (calculate number) unexpected panic attacks during the past week; is that right?

(Rater: If no, revise previous answers as needed. If yes,

UPN_____ record Number/Week).

How long did most of these unexpected panic attacks last?

UPD_____ (Duration-minutes)

How bad were most of them on the 1 to 10 scale, 1 being the least and 10 being the most uncomfortable you can imagine?

UPI_____ (Intensity - Score "0" if patient had no attacks)

B. LIMITED SYMPTOM ATTACKS:

Now, during the past week did you ever suddenly experience only 1, 2 or 3 of the symptoms on the list, without having a full panic attack? Remember, by "suddenly" I mean that the symptoms reached their maximum intensity within 10 minutes from when you first noticed they were there or were getting worse.

(Rater: If yes, have patient describe worst attack and go over list to make sure there were no more than 3 symptoms. If there were, it may qualify as a panic attack, in which case the answers in Section A may need to be revised.)

In all, during the past week, how many times did you experience episodes or spells of this limited kind? Don't include the full

TLN_____ panic attacks we already discussed. (Number/week)

1. **SITUATIONAL:**

Now of those (**insert number**) limited attacks, how many occurred when you were in or just about to go into a place or situation that, in your experience, is likely to bring on an attack?

SLN_____ **(Number/Week)**

How long did most of those episodes (the ones associated with

SLD_____ those situations) last? **(Duration-minutes)**

How bad were most of them on the 1 to 10 scale, 1 being the least and 10 being the most uncomfortable you can imagine.

SLI_____ **(Intensity - Score "0" if patient had no attacks)**

2. **UNEXPECTED:**

So then of the (**total number from B**) limited attacks you experienced during the past week, (**number from B.1**) occurred when you were in or about to go into a place or situation that, in your experience, is likely to bring on an attack, and all the others occurred when you were not in or about to go into such a place or situation? Is that correct?

(Rater: If no, clarify and revise answers to B.1 as needed. If yes, proceed.)

That would be a total of (calculate number) unexpected limited attacks during the past week; is that right?

(Rater: If no, revise previous answers as needed. If yes,

ULN_____ **record Number/Week).**

How long did most of these unexpected limited attacks last?

ULD_____ **(Duration-minutes)**

How bad were most of them on the 1 to 10 scale, 1 being the least and 10 being the most uncomfortable you can imagine.

ULI_____ **(Intensity - Score "0" if subject had no attacks)**

C. **ANTICIPATORY ANXIETY**

Now I would like to get an estimate of how much you have been worrying about having a panic attack. During the past week, approximately what percent of the time when you were awake and were not having a panic attack did you worry about having a panic attack or about going into a situation that, in your experience,

AAT_____ is likely to bring on an attack? **(% time)**

How many separate times during the past week did you have periods of worry about having a panic attack or about going into a
AAN_____ situation that might cause a panic attack? (Number/week)

On the average, how anxious or nervous were you during those times? Rate your anxiety or nervousness on a scale of 1 to 10, with 1 being the least and 10 being the most anxious or nervous you can imagine? (Intensity - Score "0" if subject had no
AAI_____ attacks)

Appendix B

Because of the copyright restrictions and price, a copy of the Anxiety Disorders Inventory Schedule-Fear could not be obtained.

Appendix C

THE MOBILITY INVENTORY FOR AGORAPHOBIA

Name: _____ Date: _____

Please indicate the degree to which you avoid the following places or situations because of discomfort or anxiety. Rate your amount of avoidance when you are with a trusted companion and when you are alone. Do this by using the following scale.

1. Never avoid
2. Rarely avoid
3. Avoid about half the time
4. Avoid most of the time
5. Always avoid

(You may use numbers half-way between those listed when you think it is appropriate. For example, 3 1/2 or 4 1/2.

Write your score in the blanks for each situation or place under both conditions: when accompanied, and, when alone. Leave blank those situations that do not apply to you.

PLACES	When accompanied	When alone
Theatres	_____	_____
Supermarkets	_____	_____
Classrooms	_____	_____
Department stores		
Restaurants	_____	_____
Museums	_____	_____
Elevators	_____	_____
Auditoriums or stadiums	_____	_____
Parking garages	_____	_____
High places Tell how high. _____	_____	_____
Bridges or tunnels		

Open spaces:		
(A) Outside (e.g. fields, wide streets, courtyards)	_____	_____
(B) Inside (e.g. large rooms, lobbies)	_____	_____
Riding In:		
(A) Buses	_____	_____
(B) Trains	_____	_____
(C) Subways	_____	_____
(D) Airplanes	_____	_____
(E) Boats	_____	_____
Driving or riding in car:		
(A) At any time	_____	_____
(B) On expressways	_____	_____
SITUATIONS		
Standing in lines	_____	_____
Crossing bridges	_____	_____
Parties or social gatherings	_____	_____
Walking on the street	_____	_____
Staying at home alone	N/A	_____
Being far away from home	_____	_____
Other (specify)	_____	_____

We define a panic attack as:

(1) a high level of anxiety accompanied by
(2) strong body reactions (heart palpitations, sweating, muscle tremors, dizziness, nausea) with
(3) the temporary loss of the ability to plan, think, or reason and
(4) the intense desire to escape or flee the situation. (Note, this is different from high anxiety or fear alone.)

Please indicate the total number of panic attacks you have had in the last 7 days._____

Appendix D

ANXIETY SENSITIVITY INDEX

Name: _____

Age: _____ Date: _____ Sex: M____ F____

Listed below are a number of statements describing a set of beliefs. Please read each statement carefully and, on the 0-5 scale given, indicate how much you think each statement is typical of you.

-----0----------1----------2----------3----------4----------5-----

Strongly Disagree	Moderately Disagree	Slightly Disagree	Slightly Agree	Moderately Agree	Strongly Agree

_____ 1. It is important to me not to appear nervous.

_____ 2. When I cannot keep my mind on a task, I worry that I might be going crazy.

_____ 3. It scares me when I feel 'shaky' (trembling).

_____ 4. It scares me when I feel faint.

_____ 5. It is important to me to stay in control of my emotions.

_____ 6. It scares me when my heart beats rapidly.

_____ 7. It embarrasses me when my stomach growls.

_____ 8. It scares me when I am nauseous.

_____ 9. When I notice that my heart is beating rapidly, I worry that I might have a heart attack.

_____10. It scares me when I become short of breath.

_____11. When my stomach is upset, I worry that I might be seriously ill.

_____12. It scares me when I am unable to keep my mind on a task.

_____13. Other people notice when I feel shaky.

_____14. Unusual body sensations scare me.

_____16. It scares me when I am nervous.

Appendix E

AGORAPHOBIC COGNITIONS QUESTIONNAIRE

Name:_____ Date:_____

Below are some thoughts or ideas that may pass through people's minds when they are nervous or frightened. Please rate how often each thought occurs to you when you are nervous. Do this by writing the appropriate number from the following scale in the space next to the thought.

1. Thought never occurs.
2. Thought rarely occurs.
3. Thought occurs during half of the times I am nervous.
4. Thought usually occurs.
5. Thought always occurs when I am nervous.

_____ I am going to throw up.

_____ I am going to pass out.

_____ I must have a brain tumor.

_____ I will have a heart attack.

_____ I will choke to death.

_____ I am going to act foolish.

_____ I am going blind.

_____ I will not be able to control myself.

_____ I will hurt someone.

_____ I am going to have a stroke.

_____ I am going to go crazy.

_____ I am going to scream.

_____ I am going to babble or talk funny.

_____ I will be paralyzed by fear.

_____ [illegible]

Appendix F

EMOTIONAL CONTROL QUESTIONNAIRE

Name: _____

Age: _____ Date: _____ Sex: M ___ F ___

Listed below are a number of statements describing a set of beliefs. Please read each statement carefully and, on the 0-5 scale given, indicate how much you think each statement is typical of you.

0	1	2	3	4	5
Strongly Disagree	Moderately Disagree	Slightly Disagree	Slightly Agree	Moderately Agree	Strongly Agree

_____1. I can control the degree to which I react to particular situations.

_____2. How well I cope with difficult situations depends on whether I have outside help.

_____3. When I am put under stress, I am likely to lose control.

_____4. I can easily turn a difficult situation into a manageable one.

_____5. My emotions seem to have a life of their own.

_____6. I can deal successfully with stressful situations.

_____7. Whether I can successfully escape a frightening situation is always a matter of chance with me.

_____8. I can usually influence the degree to which a situation is potentially threatening to me.

_____9. The degree to which I react to problems is out of my control.

____10. The extent to which a difficult situation resolves itself has nothing to do with my actions.

____11. There is nothing I can do to stop anxiety once it has started.

____12. Any little thing can make me uptight.

____13. I feel like I am the victim of my emotions.

____15. I am able to prevent myself from becoming overly anxious.

Appendix G

BDI

Date: _____

Name: _____ Marital Status: _____ Age _____ Sex _____

Occupation: _____ Education: _____

This questionnaire consists of 21 groups of statements. After reading each group of statements carefully, circle the number (0, 1, 2 or 3) next to the one statement in each group which best describes the way you have been feeling the **past week**, including today. If several statements within a group seem to apply equally well, circle each one. **Be sure to read all the statements in each group before making your choice.**

1
- 0 I do not feel sad.
- 1 I feel [illegible]
- 2 [illegible] all the time and I can't snap out of it.
- 3 I am so sad or unhappy that I can't stand it.

2
- 0 I am not particularly discouraged about the future.
- 1 I feel discouraged about the future.
- 2 I feel I have nothing to look forward to.
- 3 I feel the future is hopeless and that things cannot improve.

3
- 0 I do not feel like a failure.
- 1 I feel I have failed more than the average person.
- 2 As I look back on my life, all I can see is a lot of failures.
- 3 I feel I am a complete failure as a person.

4
- 0 I get as much satisfaction out of things as I used to.
- 1 I don't enjoy things the way I used to.
- 2 I don't get real satisfaction out of anything anymore.
- 3 I am dissatisfied or bored with everything.

5
- 0 I don't feel particularly guilty.
- 1 I feel guilty a good part of the time.
- 2 I feel quite guilty most of the time.
- 3 I feel guilty all of the time.

6
- 0 I don't feel I am being punished.
- 1 I feel I may be punished.
- 2 I expect to be punished.
- 3 I feel I am being punished.

7
- 0 I don't feel disappointed in myself.
- 1 I am disappointed in myself.
- 2 I am disgusted with myself.
- 3 I hate myself.

8
- 0 I don't feel I am worse than anybody else.
- 1 I am critical [illegible] mistakes.
- 2 I blame myself [illegible] faults.
- 3 I blame myself [illegible] that happens.

9
- 0 I don't have any thoughts of killing myself.
- 1 I have thoughts of killing myself, but I would not carry them out.
- 2 I would like to kill myself.
- 3 I would kill myself if I had the chance.

10
- 0 I don't cry any more than usual.
- 1 I cry more now than I used to.
- 2 I cry all the time now.
- 3 I used to be able to cry, but now I can't cry even though I want to.

11
- 0 I am no more irritated now than I ever am.
- 1 I get annoyed or irritated more easily than I used to.
- 2 I feel irritated [illegible]
- 3 I don't get irritated at all by the things that used to irritate me.

12
- 0 I have not lost interest in other people.
- 1 I am less interested in other people than I used to be.
- 2 I have lost most of my interest in other people.
- 3 I have lost all of my interest in other people.

13
- 0 I make decisions about as well as I ever could.
- 1 I put off making decisions more than I used to.
- 2 I have [illegible]

CONTINUED ON BACK

14
0 I don't feel I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel that there are permanent changes in my appearance that make me look unattractive.
3 I believe that I look ugly.

15
0 I can work about as well as before.
1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.

16
0 I can sleep as well as usual.
1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than I used to and cannot get back to sleep.

17
0 I don't get more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.

18
0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.

19
0 I haven't lost much weight, if any, lately.
1 I have lost more than 5 pounds.
2 I have lost more than 10 pounds.
3 I have lost more than 15 pounds.

I am purposely trying to lose weight by eating less. Yes _____ No _____

20
0 I am no more worried about my health than usual.
1 I am worried about physical problems such as aches and pains; or upset stomach; or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think about anything else.

21
0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

_____ Subtotal Page 2

_____ Subtotal Page 1

_____ Total Score

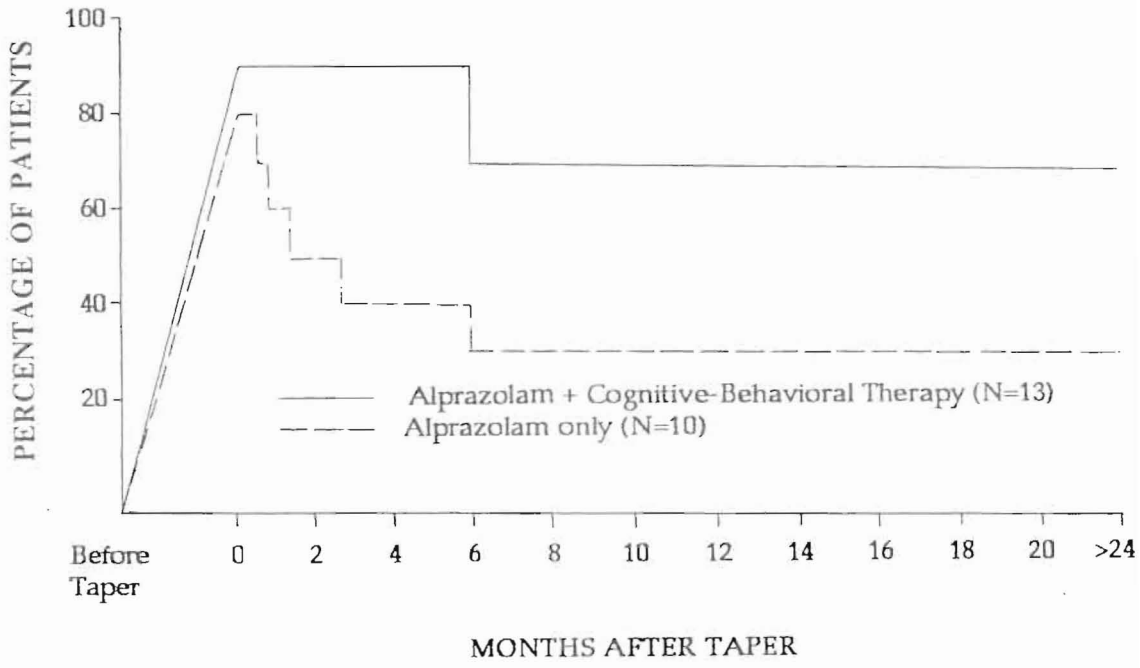
Figure Legend and Footnote

FIGURE 1. Percentage of Patients Achieving and Maintaining Drug and Other PDA Treatment Abstinence in Alprazolam-Only and Alprazolam Plus Cognitive-Behavioral Therapy Groups at 24 to 48-Month Follow-Up.[1]

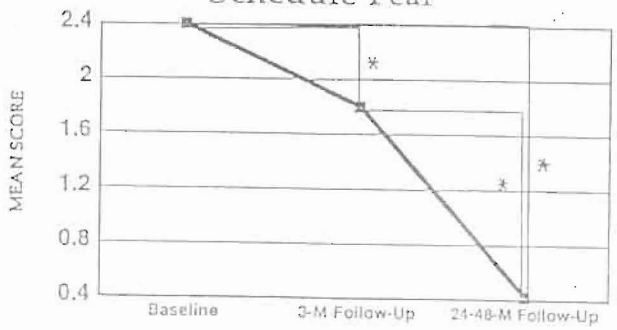
Footnote:

[1]Significant difference between survival distributions from before taper to 24-48 months after taper (Lee-Desu statistic=10.539, df=1, $p<0.005$).

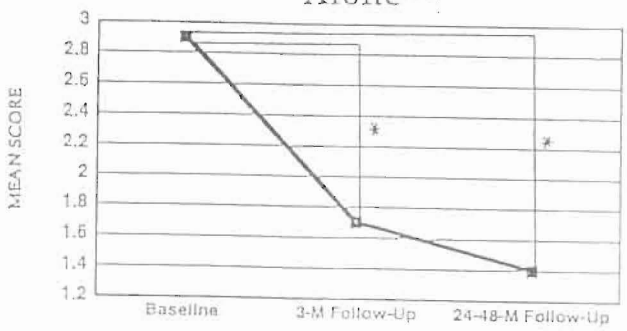
FIGURES 2-8. Changes in Mean Scores on Self-Report and Clinician-Rated Measures at Baseline, 3-Month Follow-Up, and 24-48-Month Follow-Up in the Combined Treatment Group (Significance Differences Denoted by *).


PERCENTAGE OF PATIENTS
100
80
60
40
20
Alprazolam + Cognitive-Behavioral Therapy (N=13)
Alprazolam only (N=10)
Before Taper
0
2
4
6
8
10
12
14
16
18
20
>24
MONTHS AFTER TAPER

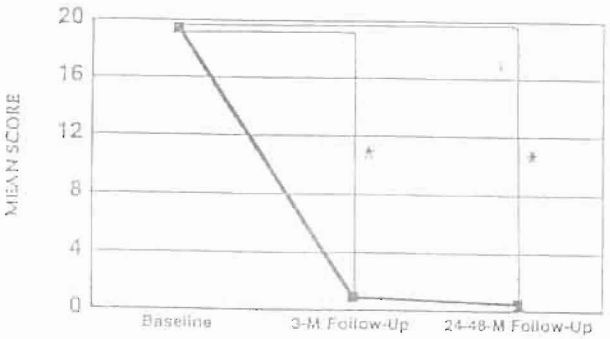
2. Anxiety Disorders Interview Schedule-Fear



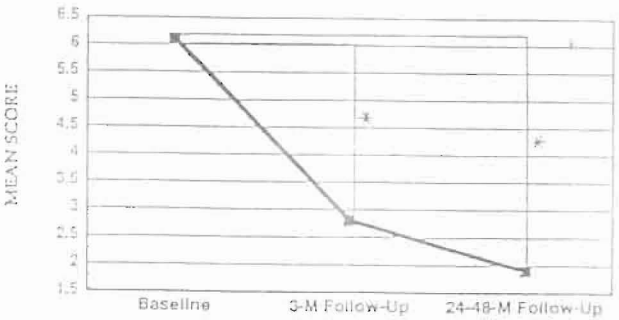
3. Mobility Inventory Agoraphobia - Alone



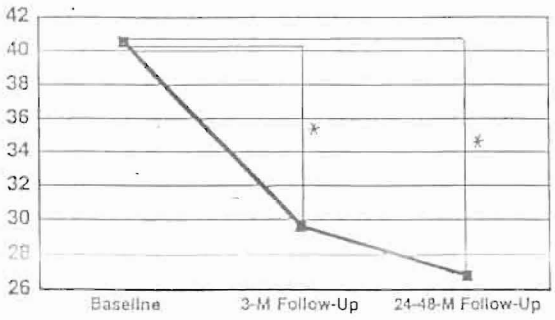
4. Anticipatory Anxiety



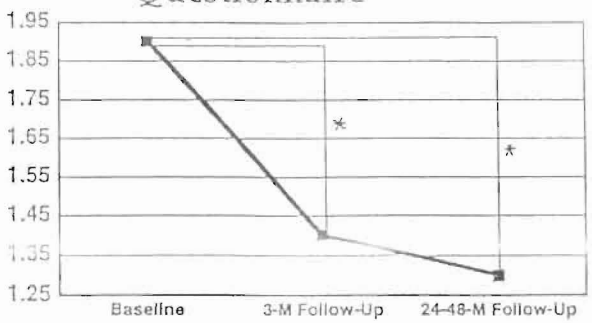
5. Beck Depression Inventory



6. Anxiety Sensitivity Index



7. Agoraphobic Cognitions Questionnaire



8. Emotional Control Questionnaire