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Predictors of Relapse and Long-Term Recovery

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Running Head: PREDICTORS OF RELAPSE AND LONG-TERM

Predictors of Relapse and Long-Term Recovery in Panic Disorder

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Abstract

Previous studies on panic disorder (Bruce et al., 1995) have examined predictors of relapse on a short-term basis. This study investigated predictors of relapse and *long-term* recovery in panic disorder treated with alprazolam or alprazolam plus cognitive behavior therapy (CBT). Relapse was defined as a return to medication or other treatment after discontinuation. Logistic regression analysis tested five variables derived from different conceptualizations of panic disorder etiology and treatment to determine if any predictors of relapse versus long-term recovery could be found. Only the change in Anxiety Sensitivity Index score from baseline to posttaper was found to be significant ($p < 0.05$, $B = 0.22$, $df = 1$, $R = 0.25$). This univariate model correctly classified 73 percent of patient outcomes at a two to four year followup. This finding suggests that a focus on cognitive change during treatment may help prevent relapse. Future research should include controlled studies to isolate the mechanism of cognitive change.

Acknowledgments

As I write this acknowledgment page at the end of my project, I must admit that I had not originally realized how much I would come to depend on other people during the course of my research. I am indebted to numerous people for their help, advice, and support on this project.

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Predictors of Relapse and Long-Term Recovery in Panic Disorder

Background

Panic disorder is an anxiety disorder in which victims experience attacks of symptoms such as a sudden feeling of impending doom, heart palpitations, shortness of breath, dizziness, trembling, nausea, as well as other fearful sensations. These attacks seem to come out of nowhere and will last for several minutes. In order to be diagnosed with panic disorder, a patient must experience four attacks within a four-week period or one attack followed by at least one month of anxiety about experiencing another (Gitlin, 1990). According to the DSM-III-R (American Psychiatric Association, 1987), at least four of the following symptoms must be present to warrant a diagnosis of panic disorder: trembling, sweating, shortness of breath, depersonalization, fear of dying, chest pain, or heart palpitations, among others. Because patients fear having another attack, they will often avoid situations in which they have had previous attacks, as well as situations in which they fear another attack. This avoidance is termed agoraphobia. Panic disorder with agoraphobia (PDA) afflicts one to two percent of the U.S. population, with an average age of onset in young adulthood. The cause of this disorder is not yet entirely clear, although a combination of biological and cognitive features has been implicated (Gitlin,1990).

Clark (1986) emphasizes the importance of catastrophic cognitive interpretations in the perpetuation of the disorder. According to Clark, panic attack victims misinterpret the benign

physical responses associated with anxiety as being more dangerous than they really are. Thus, a person susceptible to panic disorder would interpret palpitations as a sign of an imminent heart attack. According to Clark's model of panic disorder, the victim can perceive both internal and external stimuli as a threat. This perception will result in a state of apprehension, which is accompanied by various bodily sensations. If the victim interprets these sensations in a catastrophic fashion, the apprehension increases, which in turn increases the bodily sensations. The cycle continues, finally culminating in a panic attack and escape or avoidance. In other words, according to Clark, a "fear of fear" is primarily responsible for the perpetuation of panic disorder (Figure 1).

Insert Figure 1 about here.

Two major types of treatment for panic disorder are medicinal and non-medicinal. Of the medicinal treatments, benzodiazepines such as alprazolam are the most frequently used. One advantage of benzodiazepines in the treatment of panic disorder is their rapid onset of action. In addition, the side effects of benzodiapine treatment are minimal in comparison to other types of medicinal intervention. (Ballenger et. al., 1988).

A major disadvantage of benzodiazepine treatment occurs when patients attempt to discontinue the drug. The patients are either unable to discontinue taking the drug, due to physical dependence, or they relapse soon after they stop medicinal treatment. Pecknold et. al. (1988), for example, found that 33

percent of patients are unable to discontinue the drug, and that patients who do discontinue benzodiazepine treatment have a 40 to 75 percent acute relapse rate.

A popular non-medicinal approach to treating PDA is through the use of cognitive-behavior therapy (CBT). This method of treatment exposes patients to the interoceptive cues which often lead to a panic attack through Clark's "fear of fear" cycle. During CBT, patients are instructed to engage in activities such as running in place, hyperventilation, etc., which elicit bodily sensations similar to those experienced during a panic attack. Exposure to these sensations extinguishes fear of the physical feelings associated with panic attacks and decreases the chance that these physical sensations will culminate in future panic attacks. Patients are also taught to manage anxiety and reduce catastrophic reactions to it. Those receiving CBT have shown an 80 to 90 percent improvement rate out to a two year followup (Cerney et al., 1987; Craske and Barlow,1990).

Recently, cognitive-behavior therapy (CBT) has been integrated into benodiazepine therapy to see if it can aid discontinuation and prevent relapse. According to CBT formulations (e.g., Otto et al., 1992), the high rate of relapse is due to the patients' catastrophic cognitive interpretations. It is thought that the discontinuation process exposes patients to bodily sensations associated with panic during a time of increased anxiety and concern about the emergence of panic attacks. As a result, patients may begin the cycle of catastrophic interpretations posited by Clark (1986) and discussed above.

For example, Otto et. al.(l993) found that the use of CBT during the discontinuation of alprazolam significantly increased discontinuation rates from 25 percent via benzodiazepine treatment only to 77 percent in the combined treatment program. At three month follow-up, 59 percent of patients who received CBT successfully discontinued the benzodiazepine, lending preliminary support to the hypothesis that CBT may be effective in assisting discontinuation of alprazolam.

A study by Spiegel et. al. (1994) found that adjunctive CBT can also prevent acute relapse. This study found that half of the patients who underwent alprazolam discontinuation without CBT relapsed and resumed alprazolam treatment within a six month follow-up period, whereas none of the patients treated with both alprazolam and CBT experienced relapse after six months.

Finally, Hegel et. al. (1994) found that 76 percent of patients receiving the combined treatment remained medication free and 85 percent were panic free after one year. A current study (Bond and Bruce, in progress), is examining the long term success of this combined treatment out to a two to four year follow-up.

Based on the results of previous studies, then, it would appear that the combination of alprazolam and CBT has definite advantages over alprazolam treatment alone. However, while most of the research has focused on the outcome of panic disorder treatments, very few studies have examined predictors of relapse and recovery in panic disorder after treatment. Several possible predictors have been hypothesized, with some reflecting pharmacologic dependence conceptualizations of the disorder and others reflecting the types of

changes effected by CBT. A recent study investigated predictors of relapse and short-term recovery in panic disorder (Bruce et. al., 1995). In this study, change in Anxiety Sensitivity Index scores from baseline to posttaper assessments correctly classified in 85 percent of the cases as to whether patients resumed alprazolam therapy at a three month follow up or did not. The present study investigated predictors of relapse and long-term recovery on a long-term basis, at a two to four year follow-up.

Method

Participants

Twenty two participants were recruited from patients who had participated in previous treatment studies at the University of Illinois College of Medicine at Peoria Anxiety Disorders Clinic (Spiegel et al., 1994) and the Dartmouth Medical School Department of Psychiatry (Hegel et al., 1994). Each participant was re-evaluated at a two to four year followup. In the original studies, all participants met DSM III R criteria for panic disorder with agoraphobia of at least six months duration. Diagnostic assessment was done with the Anxiety Disorders Interview Schedule-Revised (DiNardo and Barlow, 1988) and the Structured Clinical Interview for DSM III-R Personality Disorders (SCID-II) (Spitzer et. al., 1990) (Appendix A).

Patients were excluded if they met DSM III-R criteria for a major mood disorder, obsessive-compulsive disorder, or an organic mental syndrome. Those patients who were medically ill, pregnant, or breast-feeding, or who had a history of psychosis or drug abuse within the past year were also excluded, as were those who were

undergoing psychotherapy; had had cognitive behavioral therapy for panic disorder in the past, or were taking medications other than alprazolam.

To be included in this study, participants must have been taking between 1 and 10 mg per day of alprazolam as their only centrally acting medication. They must also have been free of unexpected panic attacks for at least one month (4 weeks). If necessary, participants underwent a period of alprazolam stabilization before beginning the study. Participants then underwent baseline assessment, maintenance and taper of alprazolam, posttaper assessment, and followup including two to four years posttaper. The study was approved by the Institutional Review Board of the College, and all participants gave informed consent before beginning the study.

Treatments

Pharmacotherapy. All participants (n = 22) underwent identical processes of alprazolam maintenance and taper. During the taper phase, the participant's medication was decreased every seven days (extendible to 14 days) until discontinuation was complete, or until the participant requested that the dose be reduced no further. Medication was handled by a psychiatrist who was blind to the participants' group assignments. The amount of contact participants in each group had with the psychiatrist was equivalent.

Cognitive Behavior Therapy. In addition to the pharmacotherapy, some participants (n = 11) also received a form of cognitive behavior therapy developed by Barlow and Craske (Barlow and Craske, 1989; Craske and Barlow, 1990), which was

administered individually in approximately 12 weekly sessions. Included in this treatment was education about panic disorder, training in slow, diaphragmatic breathing, cognitive restructuring, and interoceptive exposure (i.e., exposure to feared bodily sensations both in and out of the clinic). The breathing training and cognitive aspects were begun during alprazolam maintenance, while interoceptive exposure was begun approximately at the same time as the beginning of alprazolam taper, so that the drug taper was complete prior to the final cognitive behavior therapy session. Participants had no contact with the therapist after the 12 sessions were completed.

Measures

Assessments were conducted at baseline (after alprazolam stabilization), posttaper (two weeks after the last successfully completed alprazolam taper step), and at various followup points out to two to four years. These assessments consisted of self-report and clinician-rated measures of the major dimensions of PDA. Clinician ratings were made by a psychiatrist blind to participants' treatment protocol.

Five measures were selected for predictive analysis that reflect different conceptualizations of relapse in panic disorder. Since one theory of panic disorder etiology posits that a cognitive change should affect discontinuation success (e.g., Clark, 1986), we chose to examine the baseline-to-posttaper change in Anxiety Sensitivity Index (ASI) scores. The ASI provides a measure of the patient' s fear of the bodily sensations related to panic.

The second measure selected was withdrawal symptom severity, since one theory of panic disorder relapse holds that patients are unable to successfully discontinue medication due to the withdrawal symptoms they subsequently experience (Rickels et al., 1993; Otto et al., 1992).

Two measures of patients' pretaper exposure to benzodiazepines were also assessed. The first was the patient' s stabilized alprazolam dose and the second was the duration of benzodiazepine use before taper. These measures were selected to reflect the theory that perhaps it is the quantity or duration of benzodiazepine use which influences who relapses and who does not.

Finally, we examined the baseline score on the Mobility Inventory for Agoraphobia as a determination of the severity of the illness (Chambless et al., 1985). This inventory measures a patient's level of avoidance when alone. The selection of this measure reflects the idea that the degree of phobic avoidance is a reliable indicator of the severity of panic disorder with agoraphobia and that pretreatment severity of the disorder may predict its relapse after treatment (Basoglu et al., 1994). (See Appendices for copies of the Mobility Inventory for Agoraphobia and the Anxiety Sensitivity Index).

Results

Predictive Analysis

Forward stepwise logistic regression (Hosmer and Lemeshow, 1989) was used to determine if any variables correctly classified patients who relapsed versus those who successfully discontinued medication through the long-term followup.

The analyses of the measures were performed with an entry criterion of $p < 0.05$. Of the five variables analyzed, only the change in ASI score from baseline to posttaper was found to be significant at $p < 0.05$ ($B = 0.22$, $df = 1$, $R = 0.25$). This univariate model correctly classified 73 percent of patient outcomes at a two to four year followup.

Discussion

This study found that the change in ASI scores from baseline to posttaper correctly classified 73 percent of the cases as to whether or not patients had relapsed at a two to four year followup. This finding supports Bruce et al. (1995), who found that a change in ASI scores from baseline to posttaper correctly classified patients' relapse in the short term (three month followup) 85 percent of the time. The present study, however, is the first to find this predictor significant in the long-term.

This finding has considerable implications for treatment. If it is indeed possible to predict what types of patients will relapse, therapists may be able to adjust their treatment programs accordingly in order to prevent this relapse from occurring. More specifically, if the technique that actually changes the ASI score can be determined, therapists may rely more heavily on this technique than on solely pharmacological treatments.

There are some problems with this study, however, which are worth noting. First, our use of a relatively small sample results in weaker statistical power, which means that generalization to the population of PDA patients should be done cautiously. In addition, it is possible that other predictors could emerge as a result of using a

larger sample size. Therefore, the results of this study should be considered preliminary findings needing replication.

Second, this study did not control for the "active" elements in treatment accounting for the change in ASI. In other words, we found a significant correlation between a change in ASI score from baseline to posttaper, but such a correlation does not help us identify what it is in the treatment that is responsible for the change.

This study offers several directions for future research. Because this study concentrated primarily on predictors of relapse and long-term recovery in a broad range of benzodiazepine users, (i.e., those receiving alprazolam alone and those receiving alprazolam plus CBT), future research could compare predictors between the two groups in order to elucidate differences between and determine what the components in the therapies that are responsible for relapse or recovery. A similar study with a larger sample would also help increase the generalization of the present findings to the larger population. Future studies should additionally aim to identify the specific techniques that are responsible for the change in ASI. Finally, other isolated variables based on additional conceptualizations of panic disorder could be compared more specifically in an attempt to develop a composite index of long term relapse and recovery in panic disorder.

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Appendix A: Screening Measures

Due to copyright restrictions and time constraints, copies of the Anxiety Disorders Interview Schedule -- Revised and the Structured Clinical Interview for DSM III-R Personality Disorders were unavailable for this paper.

Appendix B: 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.

	When alone	When accompanied
PLACES		

Theatres _____ _____

Supermarkets _____ _____

Classrooms _____ _____

Department stores _____ _____

Restaurants _____ _____

Museums _____ _____

Elevators _____ _____

Auditoriums or stadiums _____ _____

Parking garages _____ _____

High places _____ _____

Tell how high _____

Enclosed spaces (e.g. 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 C: 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.

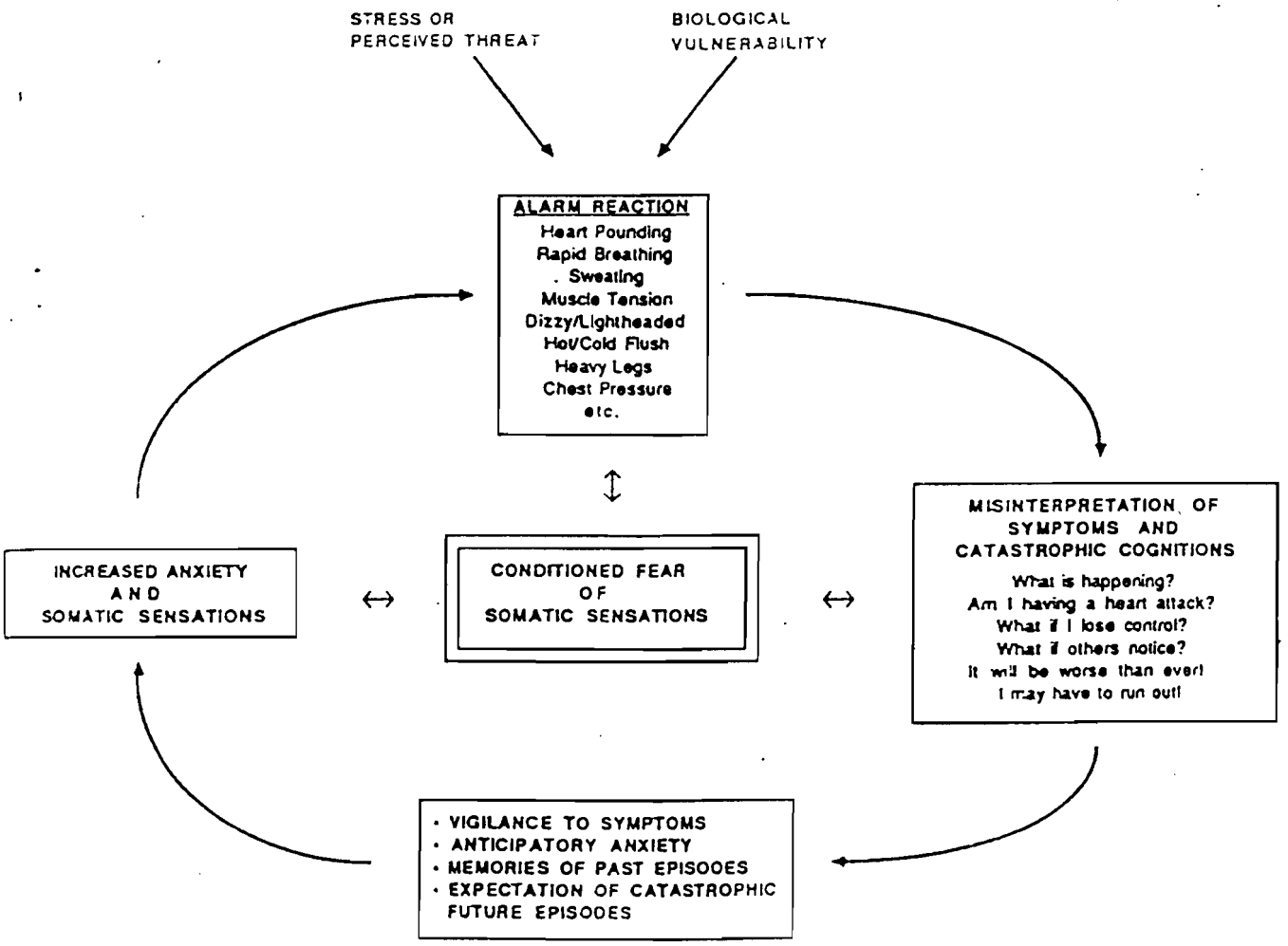
14. Unusual body sensations scare me.

15. When I am nervous, I worry that I might be mentally ill.

16. It scares me when I am nervous.

Figure Caption

Figure 1. Clark's "fear of fear" cycle, one theory for the perpetuation of panic disorder.


STRESS OR
PERCEIVED THREAT
BIOLOGICAL
VULNERABILITY
ALARM REACTION
Heart Pounding
Rapid Breathing
Sweating
Muscle Tension
Dizzy/Lightheaded
Hot/Cold Flush
Heavy Legs
Chest Pressure
etc.
MISINTERPRETATION OF
SYMPTOMS AND
CATASTROPHIC COGNITIONS
What is happening?
Am I having a heart attack?
What if I lose control?
What if others notice?
It will be worse than ever!
I may have to run out!
CONDITIONED FEAR
OF
SOMATIC SENSATIONS
INCREASED ANXIETY
AND
SOMATIC SENSATIONS
• VIGILANCE TO SYMPTOMS
• ANTICIPATORY ANXIETY
• MEMORIES OF PAST EPISODES
• EXPECTATION OF CATASTROPHIC
FUTURE EPISODES