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State-Dependent Learning During Alprazolam Assisted Exposure:

A Pilot Study of Social Phobia

Patrick B. Mc Grath

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Running head: Social Phobia

1993

Acknowledgments

First, I would like to thank Dr. Sharron Eggers for believing in me enough to set up that first meeting for me at the University of Illinois College of Medicine at Peoria (UICOMP). Without her connection there, my internship career and the "Mc Grath Model" would have never come about.

Second, I thank Melanie Mc Diarmid for driving me to Peoria for those first two semesters and sharing that internship experience with me, and helping me to mold it into what it is now. I do have some words of advice though - GET SOME NEW TAPES. I swear that if I ever hear "R.E.M." or "They Might Be Giants" again, I will scream.

Third, I would like to thank all of the other interns that have passed through the doors of UICOMP with me - Julie, Lisa, Barbie, Pam, Marygrace, Lisa, Laura, and Dianna. These "wonderful, beautiful internship goddesses" (Lisa and Julie made me say that) were great support, and fun to work with and share car rides to Peoria with (and no, Catholics do not worship idols Lisa, you man hater (ha ha), but hey, that reminds me of a joke I heard.....).

Fourth, I would like to thank the faculty and staff at UICOMP. They have been wonderful in putting up with me for the last 2½ years. Thanks to Kathy for typing up my letters for graduate school (let's hope it was not all for naught), and to Dr. Spiegel for his always encouraging words and wisdom. And last, but not least, thanks to Dr. Bruce. You guided me along and helped me to learn the ropes. You were a friend, and I will

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Finally to my family, You have been great. Thank you for the support, financially and emotionally. You may not understand the work I do, but you are interested, and I'll always appreciate it. Thank you for the pep talks and the prayers - I love you all.

O.K., one more. Thanks to the inspiring words and music of Geddy, Alex, and Neil of Rush. Some day I will meet you. And thanks to God, who in many ways through this crazy semester has been someone to turn to. Now, please get me into graduate school, and we'll take it from there.

Enjoy the paper.

P.S. To those in the basement, I deserved it!

## Abstract

Social phobia is a newly defined disorder, and treatments for it typically involve pharmacotherapy or some form of in vivo exposure. When combining these therapies, there are three possible outcomes: No effect, an additive effect, or an interference effect. If additive, the pharmacotherapy will enhance the extinction of fear, and it will not increase the chance of relapse after drug discontinuation. If there is an interference effect, the pharmacotherapy will block extinction to the phobic situation, and there will be a relapse of anxiety when placed in the phobic situation in the no drug state. If this is the result, it may be due to state-dependent learning. This study tested to see what effect the combining of a placebo or alprazolam with guided exposure would have on subjective measures of anxiety for a socially phobic patient, and to see if state-dependent learning would be present in the alprazolam + exposure condition. Results suggest that there was state-dependent learning in the alprazolam + exposure condition, and that fear extinction was greater in the placebo + exposure condition.

State-Dependent Learning During Alprazolam Assisted Exposure:

A Pilot Study of Social Phobia

Social phobia is a relatively new disorder, having first been described by Marks and Gelder (1966), and not having been formally recognized in the United States until 1980, with the publication of the Diagnostic and Statistical Manual-III (DSM-III) (American Psychiatric Association, 1980). As stated in DSM-III-R (the revised third edition) (American Psychiatric Association, 1987), social phobia is "a persistent fear of one or more situations... in which a person is exposed to possible scrutiny by others (p. 243)." Typical examples of social phobia are the fear of using public restrooms, writing or eating in front of people, and speaking in public. While in these situations, the social phobic fears embarrassing or humiliating himself.

Further criteria used to diagnose social phobia are 1) the person typically avoids or painfully endures a feared situation, 2) the avoidance interferes with social or occupational functioning, and 3) the person recognizes that the fear is excessive. Also, there may not be any relation to another Axis I (non-developmental) or Axis III (physical) disorder (American Psychiatric Association, 1987, p. 243).

In a recent review by Scholing and Emmelkamp (1990), social phobia's prevalence in the general population has been reported at ranges from .9% to 1.7% for males and 1.5% to 2.6% for females. It is also reported that studies of the age of onset suggest social phobia typically begins between the ages of 16 to 21 years old.

As reviewed by Barlow (1988), the treatment receiving the most empirical support for this disorder is in vivo exposure to the feared situation. Several researchers have reported that patients exposed to anxiety-evoking stimuli had higher rates of improvement on nearly all psychological measures than did those instructed to avoid anxious situations (Butler, 1985; Greist, Marks, Berlin, Gournay, & Noshirvani, 1980).

Another study found that a group of social phobics exposed to their anxiety provoking or "phobic" situations fared better in post-test and 3 and 6-month follow-up tests than those in a waiting list control group (Butler, Cullington, Munby, Aimes, & Gelder, 1984). In a review by Marks (1985), studies confirm that the beneficial effects of exposure are maintained up to nine months after treatment completion. Exposure can either be encouraged, which has the patient do it on his own, or it can be guided by the therapist.

The mechanism of action through which exposure has been hypothesized to work is an extinction of the phobic response. "Extinction refers to decrements in the strength of learned responses through repetition of unreinforced responding" (Barlow, 1988, p. 289). Thus, patients learn that while exposed over and over to the feared situation, the feared consequence will not occur. This process is repeated until the patient can enter the situation with no maladaptive rise in anxiety. Exposure is not a quick relief therapy. Although it takes time to complete, it appears to have lasting effects.

Pharmacotherapy is another widely used treatment for anxiety disorders

(Barlow, 1988; Mavissakalian, 1982; Barlow & Mavisakalian, 1981). One class of medications that may be used are the benzodiazepines, such as alprazolam, a triazolobenzodiazepine (Mavissakalian, 1982). Alprazolam has shown consistent anti-anxiety effects, it is relatively safe, and it is quick acting (often in a matter of days anxiety will be subdued). But, even on slow tapered schedules, relapse rates are still high, with some studies finding as high as 90% relapse (Barlow, 1988).

A third direction for research in the treatment of anxiety disorders is to investigate combinations of behavior therapy and pharmacotherapy (Telch, 1988). When combining these treatments, there are three possible outcomes. One, the combined treatments may show no difference in outcome ratings than one or the other treatments alone. If this is the result, then there is no need to combine the treatments. Two, there may be an additive effect in that both therapies are beneficial to the subject and they do not interfere with the other's mechanism of action, and there should be low relapse rates after the treatment is discontinued. If this is the outcome, the drug will have allowed for quick suppression of anxiety while the behavior therapy, which is known to have lasting effects due to extinction of the phobic response, will have been learned with no interference. Or three, there may be a negative effect; one of the two therapies may interfere with the other and inhibit its mechanism of action, and there may be a high relapse rate after treatment is discontinued. If this is the result, it is likely that the drug somehow interfered with the extinction process of the behavior therapy (Telch, 1988).

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Additive effects have been supported for tricyclic antidepressants. For example, Mavissakalian, Michelson, and Dealy (1983), found that imipramine combined with programmed practice was much more effective in the treatment of agoraphobia than was imipramine alone. They and others later found that imipramine enhanced the effects of exposure therapy for agoraphobics (Cox, Ballenger, Laria, Hobbs, Peterson, & Hucsek, 1988; Mavissakalian & Michelson, 1986).

In a review article, Wardle (1990) found that in five out of six anxiety disorder studies which she compared, the benzodiazepine + exposure groups had higher or equal outcome measure ratings to the no drug or placebo groups.

Despite these findings, authors are still calling for more research on combined treatments (Wardle, 1990; Gray, 1987; Leibowitz, Gorman, Fyer, & Klein, 1985). This is partially due to few studies found in the literature having benzodiazepines combined with exposure (Wardle, 1990), and also due to evidence of benzodiazepine's interference effects. Gray (1987), found that "under some conditions, anxiolytic drugs are able to directly and completely block the process by which exposure to an anxiogenic event creates behavioral tolerance for that event (p. 439)."

One potential interfering mechanism is the phenomenon known as state-dependent learning, which is the learning or storage of a set of behaviors in one state, such as while on alprazolam, and the later retrieval and testing of that behavior in the same or different state (Weingartner, 1978). What is learned while on a drug may not transfer to the no drug

condition. While a dispute continues over how state-dependent learning occurs, there is research to support its existence.

In an experiment of fear extinction in rats with the two benzodiazepines chlordiazepoxide and diazepam, it was found that when extinction was combined with one of the benzodiazepines, it was relatively ineffective at reducing fear in the drug free state. The rats in the combined treatment exhibited more freezing (fear) behavior than those in the no drug (extinction only) condition (Bouton, Kenny, & Rosengard, 1990).

One study done with humans found that in an alprazolam + exposure treatment program for panic disorder with agoraphobia, high-dose alprazolam significantly impaired post-exposure gains when the drug was discontinued, but not while patients were still on the drug (Marks, Swinson, Basoglu, Kuch, Noshirvani, O'Sullivan, Lelliot, Kirby, Mc Namee, Sengun, & Wickwire, in press). The exposure alone group showed improvement even through follow-up.

However, a similar study found differing results (Bruce, Spiegel, Falkin, & Nuzzarello, 1992). Bruce et al. (1992), found that an alprazolam + Panic Control Therapy group did not have significantly impaired gains after alprazolam was tapered. The combined treatment group actually fared better than the drug only group on discontinuation outcomes.

With these differing results, it can be seen that there are no conclusive studies directly investigating the role of state-dependent learning while under the influence of alprazolam in humans. Further,

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I am personally not aware of any studies comparing alprazolam + guided exposure to placebo + guided exposure for social phobia. However, a study has recently been published in which alprazolam was combined with encouraged exposure for social phobia (Gelernter, Uhde, Cimbalic, Arnkoff, Vittone, Tancer, & Bartko, 1991). Gelernter et al. (1991) concluded that when combined with encouraged exposure, alprazolam is an effective treatment for social phobia.

Therefore, this study had two goals: 1) to see if alprazolam would facilitate or interfere with guided exposure both within and between sessions, and 2) to see if there would be any evidence of state-dependent learning in the alprazolam + exposure condition. This was done by comparing the subjective units of distress (SUDS) ratings for exposure to a task while under the influence of alprazolam, and then re-exposing the patient to the same task two days later (giving the drug time to wash out of his system).

I predicted that the alprazolam + exposure conditions would have a lower rating of anxiety than the placebo + exposure conditions due to the fact that alprazolam is a fast acting benzodiazepine, and would therefore quickly reduce anxiety in the subject. I also predicted that there would be state-dependent learning. I felt that the drug effect will be similar to that of alcohol. While people typically "loosen-up" after several drinks, I predicted that the subject would be affected in a similar manner, and he would be able to perform the exposure tasks with relative ease. But, after the drug was washed out, I predicted that

the subject would be at the same anxiety level that he was at previous to drug ingestion.

#### Method

##### Subject

The subject for this study was a 25 year old socially phobic male, as defined by DSM-III-R criteria. His social phobia was of the generalized type. He was referred to the University of Illinois College of Medicine at Peoria (UICOMP) in 1989 for the treatment of social phobia with secondary depression. That is, his depression was a consequence of his fear of social situations. Because of its severity, the depression was treated first. The subject has since overcome his depression, and has entered treatment for social phobia. He agreed to participate in this study as part of a clinical assessment to determine if his exposure therapy should be assisted by medication.

##### Apparatus

All exposures were recorded through a one-way mirror. A Panasonic video camera and hidden microphone were used to record all six sessions.

Ratings of anxiety were taken using a 0-100 Likert type rating scale of subjective units of distress (SUDS). The ratings were taken before, during (at approximately thirty second intervals), and after the exposure session.

##### Procedure

This experiment lasted for 13 consecutive days, with the subject completing what will be termed six "units" of exposure to six differing

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tasks. Each unit consisted of six exposures, termed trials, to a given task.

On the morning of the first session, the subject was oriented to the self-rating scales to be used during the exposure sessions. Then, exposure to the first task (Task A) began. This first exposure was used to obtain a baseline value of anxiety for that particular task.

After the first exposure to Task A, the subject was given either .5 mg. of alprazolam, or an indistinguishable placebo pill. This was done in a double-blind fashion. Which pill the subject received was determined randomly, with three alprazolam and three placebo pills having been given out over the six exposure sessions.

Exposure to Task A took place three more times, beginning one hour after the ingestion of the pill. This length of time allowed for peak blood concentration of alprazolam (Paul, 1985).

Prior to the second exposure trial (the first exposure after the ingestion of the pill), the subject was asked if he thought he had taken alprazolam or not. This was done to see if the subject could predict whether or not he was medicated, and if he could, whether it would affect his exposure SUDS. After the three exposures, the subject was instructed to come back in the morning two days from then to continue the assessment. He was instructed not to practice the task that he had been exposed to.

The third day began with two more exposures to Task A. This was the test for state-dependence, since the drug had had adequate time to wash out of the subjects system.

The end of the last exposure to Task A marked the end of the first unit. The subject was then exposed to Task B. This cycle was continued until all six units were completed. The tasks were arranged in a hierarchy from least to most anxiety provoking.

#### Design

An alternating treatment design was used in this study. This design was optimal because it allowed for a rapid, random alteration of the two conditions, and for easy comparison of the effects of the conditions.

#### Human Subject

The subject had consented to participating in the assessment experiment, and had signed all necessary forms and documents before exposure began. All data were kept anonymous and confidential. At the end of the study, the subject was debriefed and placed into a treatment program for social phobia that was modeled after the optimal treatment phase from this study.

#### Treatment Integrity

The degree to which the exposure and medication protocols were delivered was assessed via content delivery checks of the recordings made of the sessions. All of the sessions were videotaped, and 50% were reviewed for treatment integrity. Those sessions reviewed were rated for compliance with the treatment protocol on a 0 - 100 Likert scale developed at the clinic. The therapist was rated for inappropriate verbalizations (e.g. topics irrelevant to active therapy, or particular to alternate therapies) as well.

Compliance with the medication protocol was confirmed by having the subject ingest the designated pill in front of the therapist one hour before exposure began.

### Results

To examine whether SUDS scores decreased as a function of time (habituation), thus confounding results, the percent change from baseline for the average of trials two, three, and four (active exposure therapy) of each unit was computed and graphed by condition in the order that they were presented to the subject (see Figure 1). The average percent change score remained around 50% for the first five trials, and was around 40% for the sixth trial. This consistency of response suggests that learning occurring to one task did not generalize reliably to others and result in gradual habituation as a function of time. Further, if habituation were to have occurred, there would have been an increase in percent change from baseline scores, and not a decrease as seen in the sixth trial.

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Insert Figure 1 about here  
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### Credibility

Prior to treatment, the subject was asked to rate the following question on a 0 - 100 scale; "How reasonable do you feel the treatment protocol is?". He gave the protocol a 100% credibility rating. After the study was completed, he was asked if he would recommend this protocol for a friend with social phobia, and he replied that he would.

Treatment Integrity

As described earlier, 50% of the exposure sessions were checked for treatment integrity. The results indicate that there were no integrity violations. Further, there were no instances of the medication protocol being violated. Thus, it appears that both the pharmacotherapy and exposure therapy were delivered distinctly and as intended.

Also, the patient guessed which pill had been administered to him only 44% of the time, or one correct guess above random (In the entire study done at UICOMP, there was also a beta-blocker condition which was not reported in this study. In the entire study there were nine units, and the subject guessed which pill had been administered only four times.). Thus, it appears that the subject was unable to predict whether he was medicated or had taken a placebo pill.

To test whether the conditions differed during exposure, the SUDS from the six units were averaged by condition and graphed per trial (see Figures 2 & 3). Based on the SUDS scores for day one, it can be seen that there was a large initial drop of SUDS levels in the alprazolam + exposure condition (AEC) after drug ingestion, while it was much more gradual in the placebo + exposure condition (PEC). The latencies were also considerably shorter for the first two pill + exposure trials of the AEC than for the PEC (exposure would end when three consecutive SUDS ratings of 10 were given during exposure). However, by trial four, both conditions had similar scores and latencies.

To test for possible interference effects, trials five and six (day



three results) can be graphically compared. There was moderate rebound in both conditions for the fifth trial (the first test of state-dependent learning), and a return to non-baseline exposure norms in trial six. One notable effect in the graphs is that day three latencies for the AEC were twice as long as they were for the PEC.

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Insert Figures 2 & 3 about here  
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To test whether conditions differed during exposure relative to baseline, SUDS scores were converted to a percentage change from baseline value. This allowed for comparisons of conditions without the effect of varying baseline unit scores (see Figures 4 & 5). Percent change from baseline values for mean scores (average mean of the three units in each condition per trial) and maximum scores (average maximum score of the three units in each condition per trial) of trials two and three show that the AEC had a greater initial reduction of anxiety than the PEC. By the fourth trial, the PEC is shown to have had the greatest percent change from baseline.

For the fifth trial (the first check for state-dependent learning), both conditions rebounded, or approached near baseline levels. At the sixth trial (the second check of state-dependent learning), both average percent change scores are near the highest average percent change scores (those of trial four) again for mean score averages. For maximum score averages at trial six, however, the AEC percent change score does not

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even equal that of trial two (the lowest percent change score while medicated), while the PEC score is near that of trial four.

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Insert Figures 4 & 5 about here  
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### Discussion

Any bias or expectancy effects affecting this study are unlikely, as the blind was kept, and the subject guessed only one above random as to whether he had taken a placebo or one of the medications. The treatment protocol was highly credible to the patient, and treatment was delivered distinctly and as intended. Also, there were no order or habituation effects that confounded the outcome of the study.

The first hypothesis, that alprazolam would decrease anxiety quicker than the placebo was confirmed. The AEC did have quicker reductions of anxiety than the PEC did. By the fourth trial though, the PEC had lower ratings of anxiety than the AEC did.

The second hypothesis was that there would be state-dependent learning. An interference effect was evidenced by the large rebounds of each condition between trials four and five. The evidence supporting that state-dependent learning occurred in the AEC are the longer latencies for trials five and six on day three compared to those of the PEC (see Figures 2 & 3), and also the relatively low percent change from baseline for average maximum trial score on trials five and six (see Figure 5).

One possibility for the large amount of rebound in both conditions

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on day three is that there were attributional effects. Since there was no pill given for either condition in the fifth and the sixth trial, the subject had to overcome the external attribution of not taking a pill on these trials. With a return to near high percent change from baseline average scores (mean and maximum) in the sixth trial of the PEC condition, it seems that it only took one trial to overcome this. But, the AEC also had to overcome the internal attribution of being medicated. Looking at the percent change from baseline for maximum scores for the AEC, it seems that this was not overcome by trial six.

The strength of this study was that it had good internal validity. The treatment was highly credible and integrity was good. Also, it allowed for easily defined trends on how either alprazolam or the placebo interacted with exposure therapy.

This study did have some weaknesses though. There was low external validity due to the attributional effects of no pill being given in trials five and six. Also, the procedure used in this study was very time consuming.

Some implications can be drawn from this study. It can be seen that interference can occur when combining treatments. Therefore, there is a need for designs that can effectively combine the quick relief of anxiety that pharmacotherapy has been shown to give with the lasting effects that behavior therapy has been known to achieve. One way to do this is to use a design similar to Spiegel et al. (1992). There, pharmacotherapy and exposure therapy were given simultaneously, and exposure did not

end with alprazolam discontinuation, but lasted for several weeks following discontinuation. Therefore, even if there was some state-dependent interference from the drug, it was overcome by a continuing of exposure through and after drug discontinuation. The drug was also useful in helping those who were very frightened of exposure, because it calmed them initially. As the drug was discontinued and exposure was continued, the calming effects lost due to a decrease in alprazolam were compensated by the increased confidence instilled by the behavior therapy. This is in opposition to the Marks et al. (in press) study which discontinued high dose alprazolam and exposure therapy simultaneously. This design seems to have maximized the chance for relapse, since almost every patient relapsed after discontinuation. With no further exposure after drug discontinuation, interference was not compensated for.

Future studies will have to rule out attributional effects. This can be done by giving a pill to future subjects during all trials, but varying the active drug. Also, one or two more trials (trial seven and possibly trial eight) will need to be added to see if the AEC actually equals the PEC after several more state-dependent learning checks.

Studies such as this are useful in helping to define just how to combine treatments in order to achieve the maximum benefit from both behavior therapy and pharmacotherapy. It is through these types of studies that models of treatment can be tested so that someday interference effects can be compensated for and only additive effects will be seen in therapy. Continued research is necessary to achieve these results.

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Figure Captions

Figure 1. Habituation - Order effect graph. Each bar represents the average percent change from baseline for the mean scores of trials two, three, and four per unit.

Figure 2. Exposure in the AEC. Each line represents the mean of the three AEC units SUDS scores for that trial, and is graphed by trial latency.

Figure 3. Exposure in the PEC. Each line represents the mean of the three PEC units SUDS scores for that trial, and is graphed by trial latency.

Figure 4. Mean SUDS scores per trial averaged over the three units in each condition. Point values represent the SUDS scores percent change from baseline per trial.

Figure 5. Maximum SUDS scores per trial averaged over the three units in each condition. Point values represent the SUDS scores percent change from baseline per trial.

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ORDER EFFECTS – HABITUATION  
(average percent change from baseline for mean scores  
for trials 2,3,4)

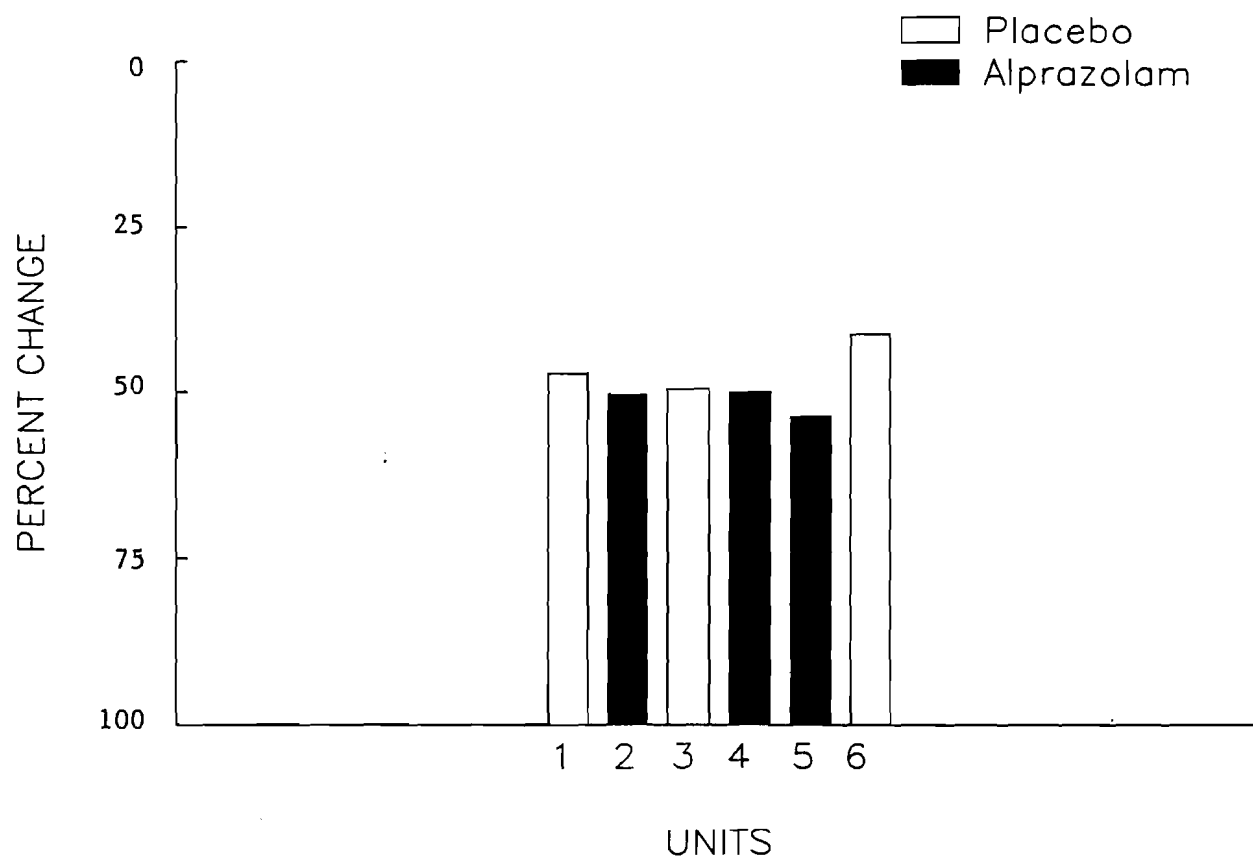


Figure 1

## Exposure with Alprazolam in a Social Phobic

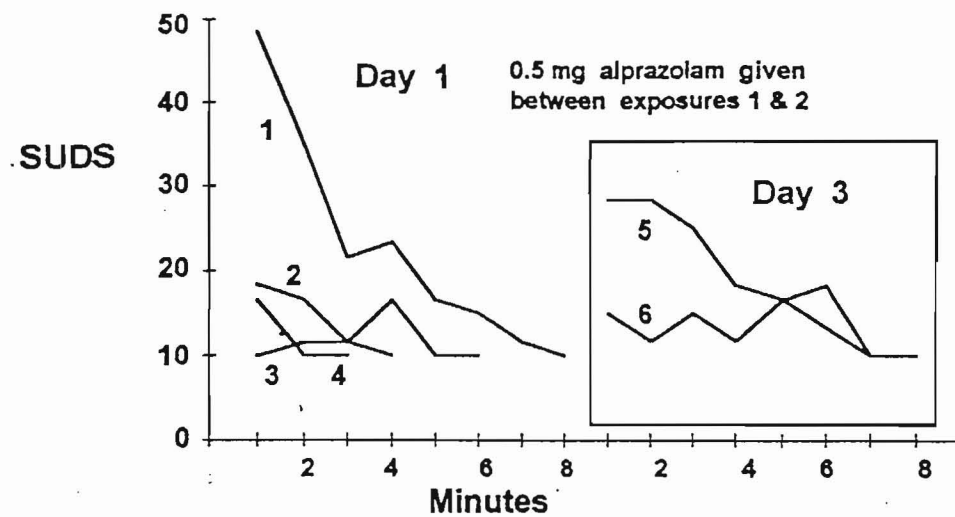


Figure 2