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ACUTE AND DELAYED EFFECTS OF ALPRAZOLAM ON FLIGHT PHOBICS DURING EXPOSURE

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Summary—In order to test if a benzodiazepine would enhance or hinder the therapeutic effects of exposure, immediate and delayed effects of alprazolam on flight phobics were assessed by questionnaires and ambulatory physiological recording. Physiological measures included heart rate, skin conductance level and fluctuations, finger temperature, respiratory sinus arrhythmia, and various respiratory measures derived from two bands calibrated for each subject. Twenty-eight women with flying phobia flew twice at a 1-week interval. One and a half hours before flight 1, 14 randomly assigned phobics received double-blind 1 mg of alprazolam and 14 received placebo. On flight 1, alprazolam reduced self-reported anxiety (5.0 vs 7.4) and symptoms (5.3 vs 8.6) more than placebo, but induced an increase in heart rate (114 vs 105 bpm) and respiratory rate (22.7 vs 18.3 breaths/min). Before flight 2, the alprazolam group did not expect to be more anxious than the placebo group (6.7 vs 6.5), but in fact indicated more anxiety during flight (8.5 vs 5.6), and a substantial increase in panic attacks from flight 1 to flight 2 (7% vs 71%). Heart rates in the alprazolam group increased further (123 bpm). Results indicate that alprazolam increases physiological activation under acute stress conditions and hinders therapeutic effects of exposure in flying phobia. © 1997 Elsevier Science Ltd

INTRODUCTION

Flying phobia is probably common in industrialized countries, with a point prevalence of 2.6% in a recent survey in Sweden (Fredrikson, Annas, Fischer & Wik, 1996). Many people with a flying phobia avoid flying because of excessive and unreasonable worries about airplane accidents, and some experience panic attacks or extreme distress during flight. It can be a specific phobia, but fear of flying is frequently a component of agoraphobia. The differentiation is sometimes difficult and concurrent diagnoses may be warranted (American Psychiatric Association, 1994).

Treatment programs with an exposure component have been shown to be effective for flying phobia (e.g., Howard, Shane & Clarke, 1983; Walder, McCracken, Herbert, James & Brewitt, 1987). Two pharmacological studies demonstrated the effectiveness of beta-blockers for lowering heart rate, but the effects on self-reported anxiety were only moderate (Campos, Solyom & Koelink, 1984; Ekeberg, Kjeldsen, Greenwood & Enger, 1990). Based on clinical experience, Taylor and Arnow (1988) recommend the acute administration of benzodiazepines for flying phobia as an effective alternative to behavior therapy.

Behavior therapists warn that combining benzodiazepines with exposure will render the exposure less effective (Sartory, 1983), but no clear-cut human evidence for this contention has been presented. Ordinarily repeated exposure to a feared situation results in a gradual successive and persistent decrement in anxiety response (Marks, 1987). Single-dose administration of diazepam enhanced this fear extinction in the treatment of simple phobia (Marks, Viswanathan, Lipsedge & Gardner, 1972) but not agoraphobia (Hafner & Marks, 1976). Chronic diazepam use did not improve the effectiveness of exposure treatment for simple phobia (Whitehead, Blackwell & Robinson, 1978) or agoraphobia (Wardle, Hayward, Higgitt, Stabl, Blizard & Gray, 1994). Animal studies suggest that benzodiazepines could be detrimental to the extinction of fear responses (Boix, Fernandez Teruel & Tobena, 1988).

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Traditional learning theory would predict that association of a drug-induced low-anxiety state with the phobic stimulus would lead to faster fear extinction (Lader & Mathews, 1968). Anxiolytics should lower anxiety in anticipation of and during confrontation with the phobic situation, reduce the unpleasantness of exposure therapy, and increase compliance (Wardle, 1990). On the other hand, benzodiazepines have a number of unpleasant side effects such as drowsiness, fatigue, ataxia, and memory disturbances (Bickel, Hughes & Higgins, 1990), which could impede extinction processes and learning efficiency during exposure.

In contrast to traditional learning theory, a recent theory of fear modification (Foa & Kozak, 1986) would predict that less 'emotional processing' and fear extinction could take place if during exposure the 'propositional fear-network' in memory is prevented from being fully triggered by anxiolytics. In particular, state-dependent learning could prevent generalization of gains from the drug to the non-drug state (Jensen & Poulsen, 1982); exposure to somatic symptoms of anxiety, blocked by medication, may be necessary to overcome anxiety (Beckham, Vrana, May, Gustafson & Smith, 1990); and patient attribution of fear reduction to the drug rather than to improvement in coping may result in a loss of gains after withdrawal of the drug (Bandura, 1977; Basoglu, Marks, Kilic, Brewin & Swinson, 1994).

In the study described below, a single dose of 1 mg alprazolam (Xanax™) was administered orally about 1.5 hr before the first of two flights. This allows peak plasma concentrations (Greenblatt & Wright, 1993) to coincide with the take-off phase of the flight. We focused in this analysis on the take-off, since it is the time of maximal anxiety for most flight phobics. Delayed drug effects were examined during the second flight 1 week later without alprazolam. Our first aim was to evaluate immediate effects of alprazolam under naturalistic conditions on subjective, autonomic, and respiratory responses of flight phobics during a flight. Our second aim was to investigate delayed effects of this single administration on a subsequent flight. Since the DSM-IV (American Psychiatric Association, 1994) explicitly includes panic attacks in the phenomenology of specific phobias, reports of panic attacks were also evaluated.

METHOD

Subjects were recruited by newspaper advertisements to participate in a study about flying phobia. Phobics were offered limited free treatment; controls were paid US$40. Twenty-eight respondents meeting criteria for a DSM-III-R diagnosis of simple phobia (flying) established with a SCID (Spitzer, Williams, Gibbon & First, 1989) and 15 controls participated in the study. Controls were selected not to have flying fears and to match phobics for sex and age. Exclusion criteria for all *Ss* were current major depression or dysthymia, cardiac or respiratory disease, psychoactive medication, or medication affecting the cardiovascular system. Phobic *Ss* were given a 10-page informational manual about flying and flying phobia, which contained a rationale for exposure therapy emphasizing that repeated exposure to a phobic situation ultimately leads to a decrease in the phobic response. It was also emphasized that researchers were not sure if anxiolytic medication enhances or decreases this exposure effect. Written informed consent was obtained from all *Ss* after the procedures were fully explained to them.

Fourteen phobics were randomized to alprazolam and 14 to placebo conditions, after matching age and severity of the phobia. Drug assignment was concealed from the experimenter and the *Ss*. Table 1 characterizes the sample. Severity of the phobia was determined by the 36-item Questionnaire on Attitudes towards Flying (QAF) (Howard *et al.*, 1983). Ages, body mass indices, and percentage exercising regularly (at least half an hour three times a week) were not significantly different between groups, nor was severity and duration of the phobia between the two groups of phobics. Three flight phobics in each condition also met diagnostic criteria for panic disorder with agoraphobia. Phobics who had used benzodiazepines during flight rated the degree to which the drug had helped them to cope with their anxiety on a scale from 0 = not at all to 10 = extremely. Groups did not differ on this scale or in the percentage of anxiety decrease attributed to benzodiazepine. None of the phobics who had previous psychological treatment had received formal behavioral treatment.

Table 1. Characteristics of alprazolam (N = 14), placebo (N = 14), and normal comparison (N = 15) groups

	Alprazolam	Placebo	Control
	Mean (SD)	Mean (SD)	Mean (SD)
Age (yr)	41.0 (8.2)	38.2 (9.9)	38.4 (11.9)
Body mass index (kg/m^2)	23.6 (4.2)	23.0 (3.6)	24.3 (4.3)
Regular exercise (%)	57	57	50
QAF (severity of flying phobia)	228 (56)	229 (51)	30 (40)[a]
Duration of flying phobia (years)	17.0 (8.4)	13.0 (11.0)	—
Panic disorder with agoraphobia (%)	21	21	0
Previous benzodiazepine use during flight (%)	57	64	0[b]
Use helped to cope with anxiety (0–10)	5.0 (3.2)	4.4 (3.4)	—
Use decreased anxiety (%)	31 (29)	37 (35)	—
Psychological treatment for fear of flying (%)	21	21	—

[a]Significant difference on t-tests between alprazolam or placebo and control.
[b]Significant difference on χ^2-tests (Yates-corrected) between alprazolam or placebo and control. No other comparison was significant.

Subjects were tested on separate days. On the day of testing, electrodes and transducers were attached and the *S* sat for 5 min in a comfortable semi-reclined chair for baseline measurements. Then, about 1.5 hr before the flight, phobics were given one capsule of alprazolam (1 mg) or placebo. Subjects were driven to international airports in San Francisco or San Jose, California, about 50 km apart, and boarded a 20-seater turbo-prop airplane operated by a commercial airline. The flight time (take-off to landing) was approximately 12 min. The experimenter drove to the destination airport, met the *S*s, and drove them back to the laboratory, which was located between the airports. One week later phobics repeated the procedure without medication.

Physiological data from the following channels was recorded ambulatorily using the Vitaport I (Becker Engineering, Karlsruhe, Germany):

1. An electrocardiogram from electrodes attached to the chest, reduced on-line, and stored as half-second epochs of heart rate.
2. Two channels of respiration using Respibands™ (Respitrace Corporation, Ardsley, NY) placed around the upper thorax and around the abdomen, which were calibrated by having *S*s breathe into a spirometer.
3. Skin conductance from the palmar surface of the middle phalanges of digits three and four of the left hand. Disposable Ag/AgCl electrodes with a contact surface area of 2.0 cm^2 and an isotonic electrode paste were used. A constant 0.5 V was applied across the electrodes.
4. Finger temperature from the palmar surface of the outer phalanx of digit five of the left hand.
5. Environmental temperature from a sensor attached to the outside of the waist pack.
6. Body movement from piezosensors attached to the right leg above the knee and to a band worn at the left wrist.
7. Barometric pressure with an altitude sensor attached to the recording unit.
8. Button presses on a marker channel.

After arriving at the laboratory on the day of flight 1, *S*s rated the plausibility of the given exposure rationale on three items ("How logical does this type of treatment seem to you?", "How confident are you that this treatment could be successful in eliminating your fear?", "How confident would you be in recommending this treatment to a friend who was extremely anxious?") on scales between 0 = not at all to 10 = very logical/confident. The three items were added to give a plausibility score. Before each flight, *S*s rated the level of anxiety they expected on SUD scales (subjective units of distress) from 0 = not at all to 10 = extremely strong. During both flights (about 3 min after take-off) and at baseline, *S*s rated their anxiety, excitement, tension, and desire to leave the situation on SUD scales. At the same time points, *S*s filled out a questionnaire asking "how they feel right now" on each of the 13 symptoms comprising the diagnostic criteria for a panic attack in the DSM-III-R (American Psychiatric Association, 1987) plus "muscle tension", "need to move bowels", and "need to urinate". Subjects rated each item from 0 = not at all to 4 = to a high degree. Before each flight, while waiting at the gate, *S*s rated their anxiety on SUD scales. Subjects rated during the first flight if they believed they had received the active medication or placebo. After that flight the experimenter rated the same

item. After both flights *S*s were asked if they had a panic attack during flight when they suddenly felt frightened, anxious, or extremely uncomfortable.

Physiological channels were analyzed off-line by computer. The take-off was identified from altitude measurements by a computer as a sudden decrease in barometric pressure. Beginning with the point of take-off, 2 min of physiological data were analyzed. Artifactual *heart rate* data points were replaced by linearly interpolated values between previous and following heart rate values where necessary. *Respiratory sinus arrhythmia* (RSA) was then computed as the natural logarithm of the spectral power density between 0.15 and 0.5 Hz using Welch's averaged periodogram method. *Movement* channels were used to assist in artifact detection in respiration and skin conductance channels. The *skin conductance* channel was analyzed as the mean level (SCL) after movement and electrode contact artifacts had been edited out. Skin conductance fluctuations were detected as changes in SCL from a zero-slope baseline exceeding 0.2 μSiemens.

The first step in analyzing the *respiration* channels was to weight and add the raw signals of the two bands to give calibrated instantaneous lung volume, coefficients for which were established by a calibration procedure (Chadha *et al.*, 1982) conducted at the beginning and end of the experiment, about 5 hr apart. Coefficients were the mean of two calibrations. The two values showed high retest reliability (R^2 for the thoracic band was 0.92 and, for the abdominal, 0.83.) A variety of respiratory parameters were computed including respiratory rate, tidal volume, minute ventilation, and duty cycle (inspiratory time/total time). Onset of inspiration and expiration were defined by slope criteria (flow rates exceeding 100 ml/sec defined onsets). Epochs containing significant movement were edited or rejected.

Statistical analysis was generally repeated-measures analysis of variance (ANOVA) with Group (alprazolam, placebo) as one factor and Flight (flight 1, flight 2) as a second, repeated-measures factor. Post hoc comparisons of means were made by the Tukey Honest Significant Difference test. Eight variables were selected a priori because of their reported sensitivity to changes in anxiety and activation and their relative independence: self-reported anxiety and excitement, number of symptoms and symptom score, heart rate, skin conductance level, respiratory rate, and minute ventilation. These were entered into an $8 \times 2 \times 2$ MANOVA with the repeated-measures factors Variable and Flight, and the factor Group. A variety of other self-report and physiological variables were summarized for descriptive purposes. Because individual symptom ratings were not normally distributed, Group × Flight interactions were computed by using Mann–Whitney *U*-tests on change scores (flight 2 minus flight 1). All *P*-values reported are two-tailed; the significance level was set to 0.05.

Following established conventions, *S*s met criteria for a panic attack during flight if:

1. they endorsed having had a 'panic attack when you suddenly felt frightened, anxious, or extremely uncomfortable';
2. SUD anxiety increased at least two points from pre-flight rating; and
3. a minimum of four DSM-III-R panic attack symptoms were rated greater than zero.

Panic attack frequency was converted to 2×2 tables and compared between groups and flights with Yates-corrected χ^2 tests, as was ability to identify the medication on the first flight. This correction makes the estimation more conservative and is usually applied when the table contains only small observed frequencies, so that some expected frequencies become less than 10.

RESULTS

The three-way Variable × Group × Flight interaction for a priori variables was significant ($F = 2.46$, $df = 7,182$, $P < 0.002$), as was the two-way Group × Flight interaction ($F = 10.4$, $df = 1,26$, $P < 0.005$). Figure 1 shows means of expected anxiety and of three of the four a priori self-report variables for the two flights. Means and standard deviations of the other self-report variables are given in Table 2. *F*-ratios and results of post hoc tests are given in Table 3. All self-report variables except excitement and expected anxiety showed a significant two-way interaction. Self-reported anxiety and predicted anxiety showed a Flight effect.

Figure 2 shows means of a priori physiological variables during the two flights. Means and standard deviations of the other physiological variables are given in Table 2. *F*-ratios and results

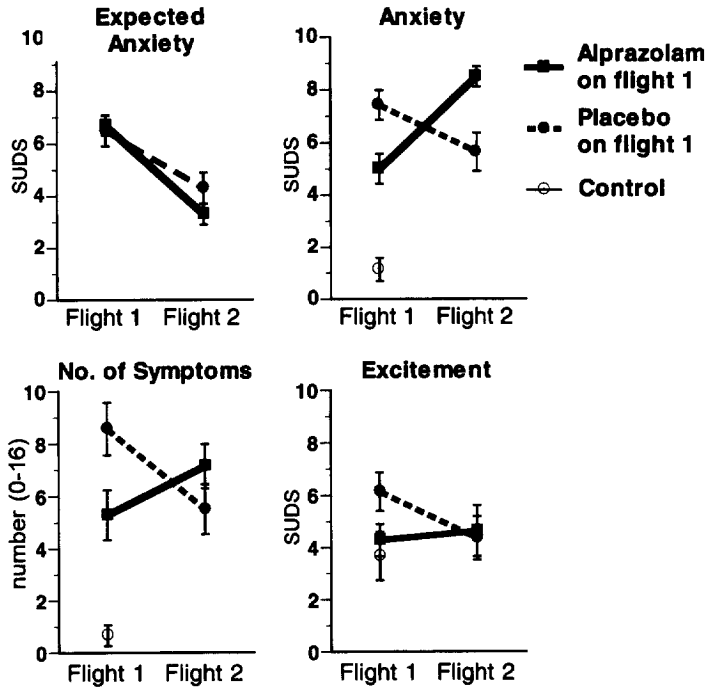

Fig. 1. Means and standard errors of four self-report measures from flying phobics who took alprazolam (N = 14) and placebo (N = 14) prior to flight 1. Means from controls (N = 15) on flight 1 are given for comparison.

of post hoc tests for physiological variables are given in Table 3. Only heart rate showed a significant two-way interaction. Respiratory sinus arrhythmia, respiratory rate, and duty cycle showed significant Group effects.

Figure 3 shows the pattern of symptoms during flight for the placebo and alprazolam groups. In general, symptoms were reduced from the first to the second flight in the placebo group, and increased in the alprazolam group. Change scores were significantly different ($P < 0.05$) for heart pounding or racing, shortness of breath, sweating, fear of dying, dizziness/unsteadiness/faintness, choking, and fear of going crazy or losing control.

Table 2. Mean and standard deviation (SD) of selected measures for flying phobics and normal comparison subjects during flights 1 and 2

	Phobics who received alprazolam on flight 1 (N = 14)				Phobics who received placebo on flight 1 (N = 14)				Controls (N = 15)	
	Flight 1		Flight 2		Flight 1		Flight 2		Flight 1	
Measure	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Self-report										
Tension (0–10)	3.9	1.8	7.9	2.5	7.5	2.6	5.1	3.1	0.7	1.3
Desire to leave (0–10)	3.1	2.7	6.0	2.7	5.9	3.7	4.6	4.1	0.1	0.4
Symptom score (0–4)	0.5	0.4	0.8	0.4	1.0	0.6	0.6	0.4	0.1	0.1
Autonomic										
RSA (bpm^2/Hz)[a]	0.89	1.14	1.19	1.08	1.83	0.95	2.16	0.98	1.55	1.12
SC fluctuations (N/min)[b]	16.2	20.6	9.7	2.7	19.1	27.2	12.5	4.9	8.7	3.6
Finger temperature (°C)	28.5	3.5	27.7	4.1	31.0	3.4	29.8	3.8	33.6	2.1
Respiratory										
Tidal volume (ml)	380	188	423	158	401	156	390	127	427	178
Duty cycle (ratio)	0.37	0.04	0.38	0.03	0.32	0.04	0.34	0.05	0.34	0.06
Control measures										
Environmental temperature (°C)	27.0	1.9	26.1	2.0	26.5	1.7	25.6	2.1	27.3	3.0
Movement (units)[c]	2.8	3.8	2.4	2.7	4.0	4.9	6.4	6.2	6.6	6.7

[a]RSA, respiratory sinus arrythmia; bpm, beats/min.
[b]SC, skin conductance.
[c]Movement units are arbitrary.

Table 3. Results of 2 × 2 repeated-measures analyses of variance and post hoc tests. Normal comparison subjects are not included in the analyses

	Repeated-measures analysis of variance						Post hoc pairwise comparison			
	Group (df = 1,26)		Flight (df = 1,26)		Group × Flight (df = 1,26)		Alprazolam vs placebo		Flight 1 vs flight 2	
Measure	F	P	F	P	F	P	Flight 1 (P)	Flight 2 (P)	Alprazolam (P)	Placebo (P)
Self-report										
Anxiety	0.09	—	5.05	0.03	48.04	< 0.001	< 0.001	< 0.001	< 0.001	0.01
Tension	0.28	—	2.22	—	35.57	< 0.001	< 0.001	0.006	< 0.001	0.02
Desire to leave	0.41	—	1.38	—	9.09	0.006	0.04	—	0.03	—
Excitement	0.73	—	1.14	—	2.57	—	—	—	—	—
Symptom number	0.49	—	0.96	—	15.75	< 0.001	0.005	—	—	0.009
Symptom score	0.52	—	0.33	—	18.08	< 0.001	0.003	—	—	0.01
Expected anxiety	0.42	—	56.93	< 0.001	2.63	—	—	—	< 0.001	0.002
Autonomic										
Heart rate	3.24	—	0.20	—	17.46	< 0.001	0.01	< 0.001	0.02	(0.06)
RSA[a]	7.31	0.01	3.55	—	0.94	—	0.003	0.002	—	—
SC level[b]	0.21	—	1.36	—	0.13	—	—	—	—	—
SC fluctuations[b]	0.35	—	2.17	—	0.00	—	—	—	—	—
Finger temperature	3.97	—	1.69	—	0.08	—	—	—	—	—
Respiratory										
Respiratory rate	5.01	0.03	0.65	—	0.41	—	< 0.001	0.003	—	—
Minute ventilation	3.67	—	2.75	—	0.00	—	—	—	—	—
Tidal volume	0.01	—	0.34	—	0.91	—	—	—	—	—
Duty cycle	9.57	0.005	3.64	—	0.87	—	0.002	0.04	—	—
Control measures										
Environmental temperature	1.06	—	2.79	—	0.00	—	—	—	—	—
Movement	3.25	—	1.11	—	2.26	—	—	—	—	—

[a]RSA, respiratory sinus arrhythmia.
[b]SC, skin conductance.

Figure 4 shows how many percent of the phobics in the placebo and alprazolam groups panicked during flight. Percentages were not significantly different during the first flight (χ^2 = 3.05, df = 1, P > 0.08) and during the second flight (χ^2 = 3.57, df = 1, P > 0.05). Panic attacks were not significantly reduced from the first to the second flight in the placebo group (χ^2 = 0.16, df = 1, P > 0.6), but the increase in panic attacks in the alprazolam group was sig-

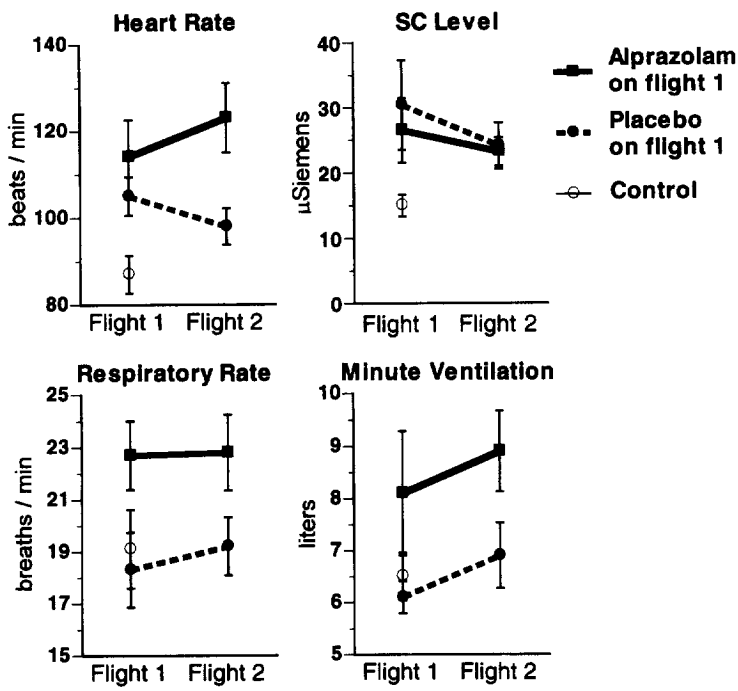

Fig. 2. Means and standard errors of four physiological measures from flying phobics who took alprazolam (N = 14) and placebo (N = 14) prior to flight 1. Means from controls (N = 15) on flight 1 are given for comparison. SC, skin conductance.

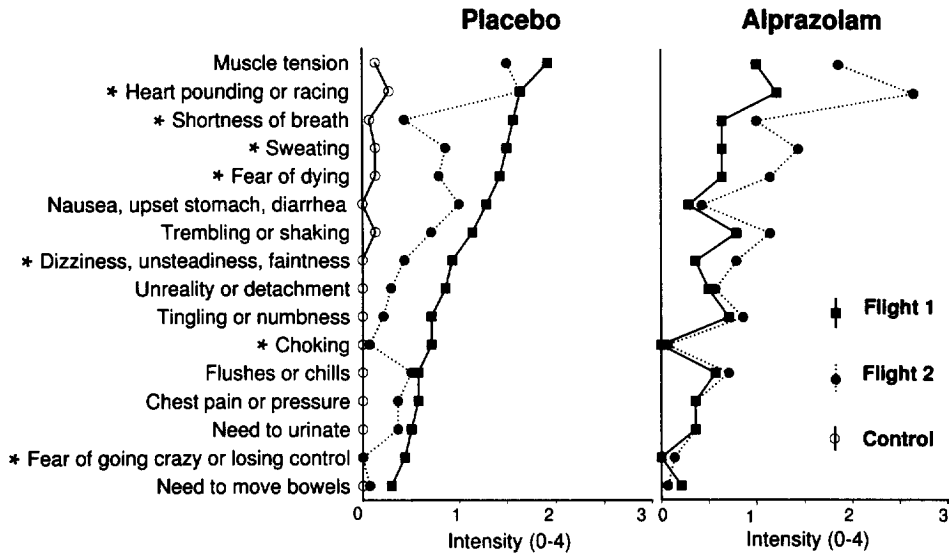

Fig. 3. Mean intensity of 16 self-reported anxiety symptoms from flying phobics who took alprazolam (N = 14) and placebo (N = 14) prior to flight 1. Symptoms are listed in order of intensity for the placebo group on the first flight. Means from controls (N = 15) on flight 1 are given for comparison but were not included in the statistical analyses. Symptoms marked with asterisks show significant differences between the two drug conditions for the flight 2 minus flight 1 change scores as explained in the text.

nificant (χ^2 = 9.58, df = 1, P < 0.005). None of the controls reported panic attacks during flight.

None of the measures listed in Table 3 differed significantly between alprazolam and placebo groups during baseline before both flights. For example, for flight 1 self-reported anxiety had a t-value (df = 26) of 0.50, number of symptoms of 0.24, heart rate of 0.34, and respiratory rate of 0.38. For flight 2 corresponding t-values were 0.32, 0.30, 0.27, and 0.50.

Subjects and experimenter could accurately guess in most cases which drug had been administered (*Ss*: χ^2 = 8.1, df = 1, P < 0.005; experimenter: χ^2 = 13.7, df = 1, P < 0.0003). Subjects identified 82% correctly (chance level is 50%), with a sensitivity of 93% and a specificity of

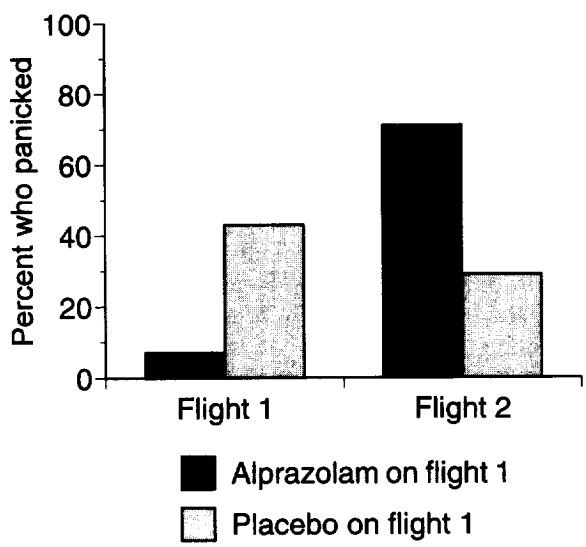

Fig. 4. Percentage of flying phobics who took alprazolam (N = 14) and placebo (N = 14) prior to flight 1 who panicked during flight 1 or 2.

71%. The experimenter identified 93% correctly, with a sensitivity and specificity of 93%. Ratings of the plausibility of the exposure rationale were not different between the alprazolam and placebo group (alprazolam: 25.0 (4.6), placebo: 25.1 (4.7), $t = 0.08$, $df = 26$, $P > 0.94$).

DISCUSSION

Our results indicate that administration of alprazolam acutely reduces self-reported anxiety, tension, desire to leave, and symptom number and score in flight phobics to a clinically and statistically significant degree, although these measures were still well above levels experienced by non-anxious controls. Delayed effects of alprazolam on a second flight 1 week later without medication showed that the anxiolytic effects of the drug were not maintained. Rather the group that had received alprazolam on the first flight did not show any signs of fear extinction, whereas the placebo group did. This delayed effect was apparent in self-report measures including a wide variety of individual symptoms. It was corroborated by heart rate—a standard physiological measure of anxiety that has been shown to distinguish well between anxious and non-anxious states (Nesse, Curtis, Thyer, McCann, Huber-Smith & Knopf, 1985; Sartory, Roth & Kopell, 1992). In the placebo group self-reported anxiety, tension, and symptom number and score decreased significantly from the first to the second flight, whereas in the alprazolam group self-reported anxiety, tension, desire to leave, panic attacks, and heart rate showed a significant increase. On the second flight, self-reported anxiety, tension, and heart rate were subsequently higher for alprazolam than for placebo.

Alprazolam apparently caused a dissociation of physiological and subjective measures. Although patients on alprazolam reported being less anxious, their physiological activation as measured by heart and respiratory rate was in fact increased. This undesirable effect of alprazolam under acute stress conditions has not been documented. Based on testing under non-phobic conditions, alprazolam was believed to have no negative cardiovascular side effects (Taylor & Hayward, 1990).

Since RSA was reduced on alprazolam, heart rate increase may have been due to a vagolytic effect of alprazolam. A similar effect has been noted for lorazepam (Vogel, L.R., *et al.*: poster presented at the 33rd Annual Meeting of the American College of Neuropsychopharmacology, 1994). However, inferences from RSA measurements to vagal control of heart rate have to be interpreted with caution if groups differ in respiratory rates (Grossman, Karemaker & Wieling, 1991). Increased respiratory rate leads to an underestimation of vagal control of heart rate.

Respiratory rate and duty cycle were significantly higher for alprazolam than for placebo on both flights. On the first flight higher levels may have resulted from alprazolam effects on the central regulation of respiration. Although benzodiazepines are thought to be respiratory depressants under baseline conditions, this effect has not been confirmed for oral administration (Mak, Wang, Cheong & Poh, 1993) and has not been generalized to acute anxiety provocations. Oddly, shortness of breath was rated as less intense under alprazolam in spite of the higher respiratory rate. On the second flight elevated respiratory rate and duty cycle in the phobics that had received alprazolam on the first flight may have resulted from higher anxiety in the alprazolam group or a carryover effect from the first flight due to classical conditioning. Perhaps by chance *S*s with higher respiratory rate and duty cycle were assigned more often to the alprazolam group, but since pre-flight baseline values of these measures did not differ, this seems unlikely. Neither did groups differ in the severity of the phobia or the proportion of comorbid panic disorder, which could be associated with chronic hyperventilation and increased respiratory rate under phobic conditions (Boiten, Frijda & Wientjes, 1994).

Skin conductance level and fluctuations, and finger temperature reflected neither anxiety nor drug group. Since skin conductance is tightly coupled to the temperature regulation system, it may not follow activation levels accurately, particularly under ambulatory conditions. Although environmental temperatures in the airplane did not differ between groups and flights, vasoconstriction from fear could lower skin temperature and reduce sweat gland activity. In addition, skin conductance levels may be more liable to ceiling effects than is heart rate.

Since fear extinction was obviously not promoted by classical conditioning of the drug-induced low-anxiety state, state-dependent learning and impeded exposure to anxiety are left as the most plausible explanations for the alprazolam group not showing an anxiety decrease on the second flight. Learning on the first flight during the mental state generated by alprazolam may not have generalized well to the second flight (Nakagawa, Iwasaki, Ishima & Kimura, 1993). In addition, according to Foa and Kozac (1986), successful exposure requires the experiencing of substantial anxiety, and in our study that experiencing was less under alprazolam.

Although the drug was given double-blind, phobics were very successful in guessing its identity, opening the door for differential expectations. However, expected anxiety was equivalent in our experimental groups for both flights. Furthermore, it decreased to the same extent for the second flight, in accordance with the exposure rationale that both groups found equally plausible. Both phobic groups had a similar history of benzodiazepine use and benefit and were likely not to have developed different personal preferences for drug versus exposure. Thus, regular expectancy effects must not have played a major role.

In contrast, an 'inverse' expectancy effect may have caused the remarkably high anxiety in the alprazolam group on the second flight. After alprazolam had effectively blocked subjective anxiety and perceived symptoms on the first flight, patients may have been alarmed by the unexpected relapse and intensity of symptoms during the second flight. This could have resulted in catastrophic cognitions and further escalation of anxiety. Such an explanation is consistent with a cognitive conceptualization of panic attacks (Clark, 1986; Margraf, Ehlers & Roth, 1986). In fact, a high percentage of patients in the alprazolam group endorsed having had a panic attack on the second flight. On the other hand, during the first flight, perception of increased heart and respiratory rate was blocked for these patients due to sedative effects of the drug. The vicious circle of anxiety was subsequently not triggered and reports of panic attacks were infrequent.

Our results indicate that the alternative treatments of benzodiazepines and exposure for flying phobia are incompatible. If patients are treated with a benzodiazepine prior to one exposure, they will have to be treated similarly prior to the next. In fact, this is the recommendation of Taylor and Arnow (1988): 0.5 or 1.0 mg of alprazolam about an hour before every flight, with an additional 0.5–1.0 mg if anxiety remains high during the flight. The alternative is to advise patients not to take medication, but encourage them to fly without it, instructing them in the principles of self-exposure.

In clinical practice, deciding between the alternatives involves weighing several factors. Setting the benzodiazepine dose at the optimal level for phobic situations is difficult. If the dose is too high, the patient will experience side effects such as sedation or ataxia. If it is too low, anxiety may not be controlled. On the other hand, some flight phobics may refuse to enter an airplane without taking a sedative drug or alcohol. So far we do not know the long-term results of either of these approaches. Will taking benzodiazepine before every flight work indefinitely or will its effect wear off, requiring increasing doses? Will repeated exposure eventually banish the fear of flying for most patients? Is pharmacological or cognitive-behavioral treatment specifically directed to unexpected panic attacks necessary for complete recovery?

Our experiment was designed to conform closely to clinical reality. However, there are several noteworthy limitations to our paradigm.

1. Alprazolam was administered at a fixed dose which may have been inappropriate for some individuals. However, the anxiolytic effect of alprazolam was significant indicating a sufficiently high dosage, in congruence with clinical guidelines. On the other hand, the symptom profile during the first flight indicates that patients had few side effects with alprazolam and were likely not overdosed.
2. The use of placebo may have decreased anxiety on the first flight somewhat and biased our results conservatively.
3. A more intensive therapist-guided cognitive-behavioral intervention more typical for manualized programs at anxiety treatment centers might have increased the efficacy of exposure.
4. The study design cannot address the question whether repeated administration of alprazolam during exposure would have improved the efficacy of the combined treatment.

5. It is not clear if a tapering schedule at the end of treatment may have led to more persistent anxiety reduction. Tapering, especially in conjunction with cognitive behavioral treatment, has been shown to be an effective strategy for preventing relapse in the treatment of panic disorder (Ballenger, Pecknold, Rickels & Sellers, 1993; Spiegel, Bruce, Gregg & Nuzzarello, 1994). In our study, informing patients about a potential relapse and appropriate coping strategies would likely have dampened the observed escalation of anxiety.

Our results are probably also valid for other phobias of the DSM-IV 'situational' subtype and panic disorder with agoraphobia, but may be less applicable to other subtypes. Studies that have looked at the interaction between alprazolam and exposure in the treatment of panic disorder with agoraphobia have given regular, several times a day doses of alprazolam, and so cannot be directly compared to our study. In clinical practice, benzodiazepines are often prescribed on an 'as needed' basis for this diagnosis, but no investigation of the efficacy of this approach has been reported. Our study casts doubt on whether such an approach would be effective in the long run.

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