Pharmacotherapeutic Treatment of Panic Disorder in Patients Presenting With Chest Pain

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While psychiatric populations with panic disorder have been shown to be responsive to several classes of psychoactive medications, there is little evidence that medical patients with panic disorder respond to similar interventions. In this nonblind, eight-week trial of alprazolam in patients presenting with chest pain and found to have panic disorder, 15 of 20 met the single criterion for improvement: a 50 percent or greater reduction in panic frequency. Several other measures were also significantly positive for those who completed the study. Furthermore, these patients reported a marginally significant drop in episodes of chest pain or discomfort. A double-blind, placebo-controlled trial is now required to test the validity of these findings.

Several recent epidemiological studies have indicated that many patients with chest pain and angiographically normal coronary arteries are likely to have panic disorder.[1–4] Beitman et al recently reported a high prevalence of panic disorder in outpatients presenting with atypical or nonanginal chest pain and no clinical evidence of coronary artery disease.[5] In psychiatric populations this disorder has been shown to be responsive to three classes of psychoactive medications, including several polycyclic antidepressants, the monoamine oxidase inhibitors, and two high-potency benzodiazepines, alprazolam which has been well studied,[6] and clonazepam,[7] as well as possibly to certain specific psychotherapeutic interventions.[8,9] A significantly positive treatment trial of chest pain patients with panic disorder would confirm the validity of the prevalence findings and serve to highlight the importance of physician awareness of the disorder, since accurate diagnosis would suggest effective treatment. There is no previous research studying the effects of known antipanic medications in chest pain patients who are found to have panic disorder without clinical evidence of heart disease.

According to the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III),[10] panic disorder is characterized by at least three attacks in three weeks of discrete periods of intense fear or discomfort accompanied by at least four of the following 14 symptoms: (1) shortness of breath (dyspnea) or smothering sensations, (2) choking or smothering sensations, (3) palpitations or accelerated heart rate (tachycardia), (4) chest pain or discomfort, (5) sweating, (6) faintness, (7) dizziness, lightheadedness, or unsteady feelings, (8) nausea or abdominal distress, (9) depersonalization or derealization, (10) numbness or tingling sensations (paresthesias), (11) flushes (hot flashes) or chills, (12) trembling or shaking, (13) fear of dying, (14) fear of going crazy or doing something uncontrolled. In addition, the symptoms cannot be explained by any organic factor.

METHODS

Subjects were recruited from cardiology outpatients with atypical or nonanginal chest pain who had no evidence of coronary artery disease and from cardiology inpatients with chest pain and angiographically normal coronary arteries. At the time of the trial the Missouri Panic-Cardiology Group was conducting epidemiological studies of panic disorder and depression in these two populations. Patients admitted to the trial all met revised DSM-III criteria (1985)[1] for panic disorder. In addition, they also had to have had at least one panic attack per week with at least three symptoms for the past three weeks. (All had to have at least one four-symptom attack, but three-

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symptom attacks to qualify subsequently, since clinically appropriate subjects might be lost with this restriction.) All patients were between the ages of 18 and 60 years, suffered no serious or uncontrolled medical illnesses, did not fit the criteria for DSM-III major depression within the past five years (unless it was judged clinically to be secondary to panic disorder), and had no history of alcohol or drug abuse in the past six months. All previous possibly psychoactive medications including β-blockers and calcium channel blockers were discontinued at least seven days before beginning the trial. Results of physical examination, clinical blood count, blood chemistry, thyroid profile, sequential multiple analysis (SMAC) and urinalysis were within normal limits.

After the screening examination, each subject was instructed in the use of the panic attack diary and kept it for one week (baseline week) without medication. Only those who had at least one three-symptom panic during the baseline week were continued on into the drug trial. All subjects entered the open-label trial of alprazolam with an initial dose of 0.5 mg/d. Vigorous efforts were made to get all patients to the most effective dose (complete elimination of panic attacks) by week 6, after which the dosage was adjusted at the discretion of the treating psychiatrist on the basis of clinical response and side effects. To be considered for evaluation a patient was required to have taken medication for at least three weeks. The acute phase of the trial lasted eight weeks. The chronic phase lasted six months followed by a taper phase, then a one-month post-taper period.

During the study subjects were rated on the Hamilton Anxiety Scale (HAM-A),[11] the Hamilton Depression Scale (HAM-D),[12] and the Physician's Global Impression (PGI).[13] Both Hamilton scores are derived from semi-structured interview questions, the responses to which were rated from 0 to 4. The scales have been shown to be valid and reliable measures for anxiety[11] and depression.[12] The HAM-A is composed of 14 items, the HAM-D is composed of 20 items. One half of each scale rates psychological symptoms and the other half rates somatic symptoms. The PGI rated degree of mental illness from 1 (normal) to 7 (among the most extremely ill patients). Subjects rated themselves on a work and social disability scale from 1 (no complaints, normal activity) to 5 (symptoms radically change or prevent normal work or social activities).

A count of the number of panic attacks experienced in the past week was also recorded at each visit, based upon the daily diaries the patients were instructed to keep. Total number of panic attacks was the sum of situational and unexpected attacks. Situational attacks were defined as those attacks occurring when the subject was in or about to be in a situation likely from his or her experience to bring on an attack. Unexpected attacks were those occurring with little or no provocation, ie, when not in a situation likely to bring on an attack. Three or more symptoms were required for an episode to be recorded as a panic attack. Patients also recorded limited symptom attacks, which were defined as any acute episode of only one or two of the panic symptoms including chest pain.

Baseline measures were paired with measures taken on each of the following weeks (weeks 1, 2, 3, 4, 6, and 8) and compared using Wilcoxon signed rank test.

RESULTS

Twenty patients with chest pain and panic disorder without evidence of significant coronary artery disease were considered for evaluation having completed the three weeks on medication. Three had angiographically normal coronary arteries (50 percent or less occlusion of a major coronary artery); 14 had normal exercise tolerance tests; one had a below normal exercise performance on exercise tolerance testing but was judged very likely to be free of significant heart disease; two had very low probabilities of coronary artery disease (1.0 percent) based upon age, sex, and chest pain type.[14,15] Two had limited phobic avoidance, and none had extensive phobic avoidance (agoraphobia). Thirteen were women and seven were men. Their mean age (±SD) was 35.8 (±9.0) years. All were white.

Five of the 20 subjects dropped out before completing the eight-week acute phase. Two subjects dropped out at the end of week 3 because of increasing severity of panic attacks and side effects. One was excluded at the end of week 4 because she made a suicide gesture with the study medication. Two refused to return after week 5, one because he still thought he had coronary artery disease and the other because he did not wish to continue to drive for two hours to the weekly appointments. One completed week 7 of the eight-week trial, requesting transfer back to her cardiologist. She is considered to have completed the study because she fulfilled all other data-collection requirements. Another 14 completed the eight-week acute trial. Therefore, 15 were considered to have completed the study. Mean dose of alprazolam for those who completed the study at week 8 was 4.30 mg ± 2.21 mg. Responders were defined as those who reported a 50 percent or greater reduction in their panic frequency between baseline and their final week in the acute trial. Fifteen of the 20 (75 percent) met this criterion. Of these 15 responders, three dropped out before reaching week 8.

Baseline measures were compared with measures for each of the subsequent weeks. These results are described in Table 1. The mean number of panic attacks from baseline to week 8 dropped from 12.80 ± 7.14 to 6.53 ± 6.45

TABLE 1. CLINICAL RATINGS FOR SUBJECTS COMPLETING THE STUDY

Variable	Week (Number of Subjects) 0 (15)	1 (15)	2 (15)	3 (15)	4 (14)	6 (15)	8 (15)
Panic attacks per week							
Mean	7.13	4.27*	3.87**	3.20**	4.00**	3.53**	2.47*
Standard deviation	6.88	5.06	5.45	5.44	6.61	6.76	5.64
Hamilton—Anxiety							
Mean	15.8	8.33*	7.67*	7.67***	6.50*	9.40**	6.27***
Standard deviation	6.96	5.00	6.54	5.31	4.31	5.86	5.01
Hamilton—Depression							
Mean	12.80	7.47*	7.40*	7.73*	6.71**	8.13*	6.53*
Standard deviation	7.14	6.84	6.66	6.04	4.94	5.72	6.45
Physician's Global Impression							
Mean	4.33*	3.33*	2.80*	2.87*	2.78*	3.00*	2.47***
Standard deviation	0.98	0.98	1.15	0.99	1.12	1.13	1.19
Patients work/social functioning							
Mean	3.53	3.00*	2.67*	3.00*	2.71*	2.87**	2.80*
Standard deviation	1.12	1.13	1.05	1.31	1.20	1.41	1.26

Note: Wilcoxon signed rank test between baseline and weeks 1, 2, 3, 4, 6, and 8
** P < .01*
*** P < .05*
**** P < .001*

($P < .01$). The number of limited symptom attacks did not change significantly. Statistically significant decreases were recorded in physician-rated measures of anxiety (Hamilton Anxiety Scale), depression (Hamilton Depression Scale), and global functioning (Physician's Global Impression scale). Patients rated themselves significantly improved in their work and social functioning. Each of these measures reached significance after week 1 and stayed significant for the eight-week acute phase.

Each subject recorded episodes of chest pain in his or her weekly diary. During baseline the 15 subjects who completed the study recorded a mean of 6.53 chest pain episodes (SD = 7.08) with a median of three episodes of chest pain or discomfort. During week 8 they recorded a mean of 5.27 chest pain episodes (SD = 12.19) with a median of 0 episodes. The mean change was −1.5 (SD = 5.28) with a median of −2 episodes (Table 2). The subject with the missing data and the subject with no chest pain episodes at both baseline and week 8 were dropped from the statistical analysis. Using a one-tailed Wilcoxon signed rank test to compare chest pain or discomfort reports at baseline with that at week 8, the difference was marginally significant, $P < .06$ ($N = 13$).

Twelve subjects entered the chronic phase. Table 3 provides a summary of their courses.

One of the subjects who completed the eight-week trial who did not respond positively to the alprazolam trial responded well to 2 mg of clonazepam per day after unsuccessful trials with desipramine and phenelzine. She soon relapsed at 6 mg per day of clonazepam, however, and entered long-term psychotherapy. Two others who did not complete the chronic phase did well on 2 to 4 mg of clonazepam per day for several months of follow-up.

TABLE 2. REPORTS OF CHEST PAIN OR DISCOMFORT BEFORE AND AFTER ALPRAZOLAM TREATMENT

Patient	Baseline	Week 8	Change
1	16	23	+7
2	26	42	+16
3	0	0	0
4	3	—*	—*
5	1	0	−1
6	1	0	−1
7	1	0	−1
8	3	0	−3
9	7	0	−7
10	12	0	−12
11	9	0	−9
12	3	1	−2
13	9	5	−4
14	4	2	−2
15	3	1	−2
Total	98	74	−21**

** Missing data*
*** P < .06 Wilcoxon signed rank test, one-tailed*

TABLE 3. SUMMARY OF COURSE OF 12 PATIENTS ENTERING THE SIX-MONTH CHRONIC PHASE OF ALPRAZOLAM TREATMENT

Number of Patients	Course Outcome
5	Completed 6-month chronic phase, taper phase, and 1-month post-taper with no difficulty
1	Completed taper phase but requested restarting at 0.25 mg alprazolam four times per day
2	Refused taper phase and requested chronic-phase maintenance
1	Refused taper phase, abused medication, and entered inpatient psychiatric treatment
1	Self-tapered between chronic phase month 1 and 2
1	Lost to follow-up after chronic phase month 1
1	Terminated after 2 months, as he was not responding to maximum dose (10 mg/d).

COMMENTS

This open-label trial of alprazolam in cardiology patients with chest pain and panic disorder without evidence of coronary artery disease suggests that this and possibly other pharmacotherapeutic interventions may be useful in medical populations generally. It is also of interest that subject reports of chest pain episodes decreased in a marginally significant way, thus suggesting that alprazolam might be useful specifically for this troublesome symptom. These suggestions must be treated cautiously for two reasons:

1. This was an open-label medication trial performed by a group invested in a positive outcome. It is likely that a placebo-controlled trial would result in a lower rate of positive response.
2. The patients entered into this trial were carefully selected. Patients with histories of major depression preceding the onset of panic disorder and those with alcohol or drug addiction histories were excluded. In addition, these subjects were committed to following a rather rigorous protocol involving weekly visits and repeated interviews and self-report questionnaires.

The next step in this process is a double-blind, placebo-controlled trial of one or two of the commonly accepted medications used for the treatment of panic disorder. Should this next study confirm the findings reported in this nonblinded study, then vigorous attempts should be undertaken to train primary care physicians and cardiologists in the recognition of the panic disorder spectrum. Without accurate diagnosis patients often go from physician to physician looking for an answer, usually running up costs for evaluations that are nonconclusive. They sometimes become convinced they have an unnamed disorder, and experience increasing social and work morbidity, as has been shown in patients with angiographically normal coronary arteries[16–18] at least one third of whom have panic disorder.[1–3] Accurate diagnosis will be likely to lead to effective treatment with a consequent reduction in social and work morbidity and in medical care costs.

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