

Use of Medication and In Vivo Exposure in Volunteers for Panic Disorder Research

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A survey of 794 subjects volunteering for studies of panic disorder with or without phobic avoidance revealed that fewer than 15% had received imipramine and fewer than 15% had undergone in vivo exposure, although the majority had engaged in some form of counseling and had used benzodiazepines. Subjects with spontaneous panic attacks reported more avoidance than subjects with situational attacks. One-half of the subjects were unemployed. The authors recommend wider use of the available effective treatments for panic disorder and phobic avoidance.

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Panic disorder with phobic avoidance is a common and disabling problem. However, in recent years effective pharmacologic and behavioral treatments have been developed. Such treatments can reduce the frequency and intensity of panic attacks and the extent of avoidance and associated problems. Tricyclic antidepressants, high-potency benzodiazepines, and monoamine oxidase inhibitors (MAOIs) have all been shown to reduce panic attacks and avoidance, at least while the medication is being used (1, 2).

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Behavioral treatments to reduce phobic avoidance have also been shown to be effective (3, 4). Furthermore, a number of authors (4–6) have suggested that combined pharmacologic and behavioral treatments may be more effective than either alone. There is evidence, however, that many patients do not receive either pharmacologic or behavioral treatment for panic disorder with avoidance. Breier et al. (7), for instance, found that although 59 of 60 agoraphobic patients had received some prior professional treatment for anxiety, only 20 patients had participated in behaviorally oriented group therapy.

The main purpose of this study was to review the previous treatment of subjects applying to participate in panic disorder research projects. The large sample also permitted us to analyze various other clinical features of panic disorder.

METHOD

From late 1983 to 1986, we sent five-page questionnaires to 1,746 subjects responding to mass media stories and requests for subjects to participate in panic disorder research studies and treatment conducted at Stanford University. Sixty percent (1,051 of 1,746) of the questionnaires were returned. Of these 1,051, some were submitted by the same people on different occasions and others contained only minimal information. After duplicate and incomplete forms were eliminated, 794 (45% of the original sample) remained and were entered into a computer for data analysis.

The first part of the questionnaire requested age, sex, marital status, employment status (and if the subject was working, current occupation), current and past medications, alcohol use, medical conditions,

panic attack symptoms, frequency of panic attacks, age at onset of panic attacks, and history of hospitalization for emotional problems. The subjects were asked to check off which of various psychotherapy procedures listed they had received. One question asked specifically if they had received training in confronting feared situations. The second part of the questionnaire, the Stanford Agoraphobia Severity Scale (8), asked the subjects to rate how they typically behaved in 10 different situations. Each situation was rated from 0 to 4, where 0="can do without anxiety," 1="can do with mild anxiety," 2="can do with severe anxiety," 3="can do only with extreme terror," and 4="cannot do under any circumstances." The 10 situations were shopping alone in a large department store, such as Macy's; being alone at home for 2 days; driving a car alone 20 miles on a freeway; waiting alone 1 mile away from a house; shopping alone in a large grocery store, such as Safeway; being alone in a crowded place, such as a movie theater or church; crossing a busy street alone; eating a complete meal alone at a restaurant like Denny's; using public transportation (e.g., bus or train) alone; and waiting in a long line at a bank or the Department of Motor Vehicles. The scores ranged from 0 to 40.

Thirty-eight patients were each given the same questionnaire within 1 month of the original submission. The percentages of agreement (number of agreements divided by agreements plus disagreements) for four questions were as follows: "Are you currently working?" 100%; "Have you ever taken any medication for anxiety or depression?" 83%; "Have you ever had a panic attack?" 100%; "Have you ever had a spontaneous panic attack?" 92%. The Spearman coefficients for the test-retest reliability of number of panic symptoms endorsed, number of panic attacks in the past week, and age of onset of panic attacks were $r=0.64$, $r=0.73$, and $r=0.56$, respectively ($df=36$). Test-retest reliability was also determined for the 10 items on the Stanford Agoraphobia Severity Scale; the Spearman coefficients ranged from $r=0.69$ to $r=0.87$ ($df=36$). The Spearman coefficient for the summed score of all 10 avoidance items was $r=0.87$, $df=36$. The percentage of subjects who rated at least three avoidance items 2 or higher on both occasions was 94%. All of these percentages of agreement and Spearman correlations are acceptable except for the age at onset of panic attacks. The ratings on the avoidance items were significantly intercorrelated; all r values exceeded 0.30. A factor analysis identified only one factor with an eigenvalue greater than 1, suggesting that the items measure one domain. In addition to the Stanford Agoraphobia Severity Scale, 50 subjects were also given the Marks-Mathews brief self-rating for phobic avoidance (9) and the phobia scale of the SCL-90 (10). The Stanford scale total score was significantly correlated with the scores on these two scales ($r=0.36$, $df=48$, $p=0.006$ and $r=0.46$, $df=48$, $p<0.001$, respectively).

TABLE 1. Marital and Employment Status of 794 Subjects Volunteering for Panic Disorder Research

Characteristic	Women (N=580)		Men (N=214)	
	N	%	N	%
Marital status				
Never married	119	21	59	28
Married	329	57	113	53
Divorced or separated	119	21	38	17
No response	13	2	5	2
Employment				
Working	182	31	100	47
Not working	227	39	52	24
No response	171	30	62	29

RESULTS

The marital and employment status of the sample can be seen in table 1. Seventy-three percent of the sample was female. The mean \pm SD age of the women was 40 ± 12.1 years, and the mean age of the men was 39.9 ± 11.4 years. Only two-thirds of the subjects reported employment status, but of those who did, 44% of the women and 66% of the men reported having jobs. There were no significant male-female differences on any of the demographic variables.

The mean \pm SD age at onset of the illness was 27.0 ± 12.5 years, and the range was 1–80 years. The mean \pm SD duration of illness was 13.0 ± 12.4 years. There was no significant difference between the women and men in age at onset (27.0 ± 12.5 versus 27.2 ± 12.7 years) or duration of illness (13.0 ± 12.5 versus 12.4 ± 12.3 years). Nearly all of the subjects said they had had panic attacks (see table 2). About 20% of both the men and women reported having been hospitalized for psychiatric problems (see table 2). The most common reason given for hospitalization was depression.

The subjects reported a mean \pm SD of 9.0 ± 3.3 panic attack symptoms (out of 14); the numbers for women and men were 9.2 ± 3.1 and 8.4 ± 3.7 , respectively. The mean \pm SD number of panic attacks in the previous 7 days was 4.5 ± 8.8 ; 159 (20%) of the subjects reported having had no panic attacks in the previous week. There was no significant difference between the numbers of panic attacks for women (4.3 ± 7.1) and men (5.1 ± 11.5). Subjects who had had spontaneous panic attacks were significantly more avoidant than patients who had not: the mean \pm SD ratings on the Stanford Agoraphobia Severity Scale were 14.6 ± 10.0 and 9.6 ± 7.9 , respectively ($t=5.6$, $df=401$, $p<0.001$, two-tailed).

The percentages of subjects who reported that they could do the specified tasks only with extreme anxiety or terror or not at all can also be seen in table 2. The most common task evoking severe phobic avoidance among the women was using public transportation, which was followed by driving alone, being in crowded places, and waiting in line. The pattern of avoidance was somewhat different for men; the task causing the most avoidance was being in crowded

TABLE 2. Histories of 794^a Subjects Volunteering for Panic Disorder Research

Characteristic	Women (N=580) ^a		Men (N=214) ^a	
	N	%	N	%
History of panic attacks				
Ever had a panic attack	565	97	202	94
Ever had a spontaneous panic attack	466	80	150	70
History of hospitalization for psychiatric problems	116	20	43	20
Previous psychological treatment				
No counseling	160	28	63	29
General counseling	228	39	84	39
Relaxation or hypnosis	79	14	38	18
In vivo exposure	22	4	7	3
Other or combination	65	11	19	9
Tasks associated with severe anxiety or terror or cannot do under any circumstances ^a				
Shopping in department store	138	34	45	30
Being alone	126	31	32	21
Driving alone	202	49	38	26
Walking alone	131	32	39	26
Shopping in grocery store	126	31	39	26
Being in crowded places	191	47	64	43
Crossing the street	91	22	24	16
Eating in public	170	41	33	22
Public transportation	220	56	60	40
Waiting in line	187	45	62	42

^aData on tasks associated with severe anxiety or terror were not available for all subjects (women, N=411; men, N=150).

places, followed by waiting in line, and using public transportation. The mean±SD score on the Stanford Agoraphobia Severity Scale was 14.3±10.1 for the women and 11.0±8.8 for the men, a significant difference ($t=3.6$, $df=533$, $p<0.001$, two-tailed).

To compare avoidant subjects with nonavoidant subjects, we defined avoidant subjects as those who rated two or more Stanford scale items as "can do with severe anxiety" or rated one item or more as "can do only with extreme terror" or "cannot do under any circumstances." The analysis was done only with subjects who completed all avoidance items (N=452). According to these criteria, 49% of the subjects (N=221) were avoidant. Only 82 (37%) of the avoidant subjects were employed, compared to 134 (58%) of the nonavoidant subjects ($\chi^2=25.2$, $df=1$, $p<0.001$). Surprisingly, fewer of the avoidant subjects than the nonavoidant subjects (20% versus 33%) were in treatment. There were no differences in medication use between the two groups.

Although the majority of men and women had engaged in some kind of treatment, few reported having used in vivo exposure therapy alone (table 2). Furthermore, only 3% of the avoidant subjects (N=6) had received in vivo exposure therapy. Although the subjects were specifically asked if they had received training in confronting their feared situations, a few might have actually had exposure therapy but classified it as "other or combination of therapies." However, at

most, only 15% of the women and 12% of the men would have received some form of in vivo exposure therapy.

Data on current medication use were available for 479 women and 183 men. Among these subjects, 55% of the women (N=262) and 44% of the men (N=81) reported using medications to treat their anxiety. Of those using medications, 77% of the women (N=202) and 73% of the men (N=59) were using benzodiazepines. Of note, only 4% of the women (N=18) and 6% of the men (N=11) were taking imipramine and only four patients were taking MAOIs. In total, only 12% of the subjects (N=82) were taking any kind of tricyclic antidepressant. Data on past medication use were available for 470 women and 179 men. Among these subjects, 62% of the women (N=290) and 54% of the men (N=97) reported having taken medications in the past. Only 3% of the women (N=12) and 4% of the men (N=8) reported having taken imipramine in the past. In total, fewer than 25% of the subjects reported having taken tricyclic antidepressants in the past or present. There were no significant differences in number of panic symptoms, number of panic attacks, or extent of avoidance between the subjects who reported current use of these medications and those who did not.

DISCUSSION

The most striking finding of this study was the apparent underutilization of two effective treatments for panic attacks and phobic avoidance: behavior therapy and imipramine. Both have been shown to be effective independently and in combination (2, 4, 6) in reducing the frequency and intensity of panic attacks and phobic avoidance. Our subjects may have underreported their past use of such treatment, but these results are consistent with those of Breier et al. (7), who also found low rates of effective treatments. MAOIs, also shown to be effective, appear to be rarely used.

It is possible that a random community sample would contain many individuals with present or past histories of panic disorder with or without agoraphobia who had received pharmacotherapy and/or behavior therapy and were no longer symptomatic. The subjects applying for research studies are obviously continuing to have problems. On the other hand, 62% of the women and 61% of the men had received some previous psychological treatment, usually general counseling, and most had received some current or past medication, usually benzodiazepines. More than likely, a random survey of a community sample would also reveal the underutilization of imipramine and in vivo exposure therapy. Our results are similar to those of Aronson et al. (11), who studied 90 subjects who called an anxiety clinic after a television show on anxiety. Relatively few had taken tricyclic antidepressants (36%), and only one had taken an MAOI. Nearly half had undergone individual psychotherapy, so these

were subjects who had not been newly identified by the mental health system. Aronson et al. did not report how many had undergone in vivo exposure therapy.

Physicians may be reluctant to prescribe imipramine and other tricyclic antidepressants for a number of reasons. Twenty-five percent or more of the patients who take imipramine experience adverse reactions or intolerable side effects even at subtherapeutic doses (3, pp. 442–444). Other patients develop dose-related side effects, such as constipation and dry mouth. While these side effects can be minimized by starting at very low doses (2), combining a high-potency benzodiazepine with imipramine when treatment is initiated (1, 2), or switching to a tricyclic with fewer anticholinergic side effects, their occurrence might make physicians reluctant to prescribe the medication. Furthermore, physicians may not be knowledgeable about the potential benefits of imipramine or other tricyclic antidepressants. Because we did not have interview data on the patients' doses and length of treatment, we did not analyze the adequacy of treatment. Breier et al. (7) and Evans et al. (12) reported that the subjects with anxiety disorder in their samples had not been given adequate trials. Thus, even when prescribed, such medication may not be given at adequate doses or for long enough.

The infrequent use of in vivo exposure is more puzzling as it is a specific, safe, and effective treatment used singly or in combination with medication (2, 3, 13). The most obvious possible reasons for its underutilization are therapists' preference for less directive psychological approaches and their lack of training in how to use it. Training in exposure therapy should be part of a psychiatric residency curriculum, and a number of available books discuss in detail how to conduct in vivo exposure therapy (2, 3, 13).

Finally, the subjects in this sample were quite dis-

abled. One-half of the subjects were unemployed, 20% had been hospitalized for psychiatric problems, the mean duration of illness was 13 years, and half the women and 40% of the men reported severe or moderately severe anxiety associated with such necessary tasks as shopping and driving.

REFERENCES

1. Ballenger JC: Pharmacotherapy of the panic disorders. *Psychopharmacol Bull* 1986; 47(suppl 6):27–32
2. Taylor CB, Arnow B: *The Nature and Treatment of Anxiety Disorders*. New York, Free Press, 1988
3. Marks I: *Fears, Phobias, and Rituals: Panic, Anxiety and Their Disorders*. New York, Oxford University Press, 1987
4. Telch MJ, Agras WS, Taylor CB, et al: Combined pharmacological and behavioral treatment for agoraphobia. *Behav Res Ther* 1985; 23:325–335
5. Mavissakalian M, Michelson L: Agoraphobia: therapy-assisted in vivo exposure and imipramine. *J Clin Psychiatry* 1986; 47: 117–122
6. Mavissakalian M: The case of psychotropic medication in combination with exposure treatment, in *Treatments of Panic and Phobias*. Edited by Hand I, Wittchen H-U. Berlin, Springer-Verlag, 1988
7. Breier A, Charney DS, Heninger GR: Agoraphobia with panic attacks. *Arch Gen Psychiatry* 1986; 43:1029–1036
8. Telch M, Michael J: *The Stanford Agoraphobia Severity Scale*. Stanford, Calif, Stanford University, Laboratory for the Study of Behavioral Medicine, 1985
9. Marks IM, Mathews AM: Brief standard self-rating for phobic patients. *Behav Res Ther* 1979; 17:263–267
10. Derogatis LR, Lipman RS, Covi L: SCL-90: an outpatient psychiatric rating scale: preliminary report. *Psychopharmacol Bull* 1973; 9:13–28
11. Aronson TA, Craig TJ, Thomas S, et al: Health care utilization patterns in panic disorder and agoraphobia: a naturalistic study in secondary prevention. *J Anxiety Disorders* 1987; 1:283–293
12. Evans L, Oei TPS, Hoey H: Prescribing patterns in agoraphobia with panic attacks. *Med J Aust* 1988; 148:74–77
13. Barlow DH: *Anxiety and Its Disorders: The Nature and Treatment of Anxiety and Panic*. New York, Guilford Press, 1988