CME Activity

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CME Objectives
After completing this CME activity, the reader will be able to:

- Identify currently available effective treatments for panic disorder
- Appreciate the importance of choosing effective medication and use an appropriate dose and duration of treatment
- Recognize that true treatment resistance is uncommon and that treatment failure is most often due to medication intolerance or inadequate medication trials.

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Dr. Cowley has received research grants from Pfizer Inc. and is a member of the Advisory Board for Eli Lilly and Company.

Ms. Ha has no significant relationships with any providers of support that may have influenced her presentation in any way.

Dr. Roy-Byrne has received grants from Bristol-Myers Squibb, Pfizer Inc., Abbott Laboratories, Eli Lilly and Company, and Zeneca Pharmaceuticals; has received honoraria from Pfizer Inc., SmithKline Beecham, and Wyeth-Ayerst Laboratories; and is a member of the Advisory Board for SmithKline Beecham and Pfizer Inc.

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Determinants of Pharmacologic Treatment Failure in Panic Disorder

Deborah S. Cowley, M.D., Eileen H. Ha, and Peter P. Roy-Byrne, M.D.

Background: We systematically assessed reasons for failure of pharmacologic treatment for panic disorder in patients referred to a specialty anxiety and mood disorders clinic and examined possible determinants of treatment-resistant panic disorder.

Method: Interview data were obtained from 106 patients with DSM-III-R panic disorder seen in consultation. Data for each of 252 past medication trials included dose, duration of treatment, side effects, outcome, and reason for discontinuation. T tests and chi-square analyses were used to compare demographic and clinical characteristics of patients failing versus responding to adequate trials and those with and without intolerable medication side effects.

Results: Of 252 medication trials, 190 used effective antipanic medications, and only 59 (23%) were adequate in dose and duration. The most common reason for treatment failure was intolerable side effects, occurring in 51 (27%) of 190 trials using effective antipanic medications. Patients discontinuing treatment due to adverse effects had higher Hamilton Rating Scale for Anxiety scores and were less likely to have a history of substance abuse. Discontinuation due to side effects was significantly more common with tricyclic antidepressants than with benzodiazepines. True treatment resistance was reported in 14 (24%) of 59 adequate medication trials. Treatment-resistant patients were younger and had a higher lifetime rate of major depression.

Conclusion: Although use of ineffective medications or inadequate trials were important factors, the most common reason for treatment failure was side effects, especially with tricyclic antidepressants. True treatment resistance was less common, since few medication trials were adequate in dose and duration, and may be associated with comorbidity.

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Received May 14, 1997; accepted Aug. 8, 1997. *From the Department of Psychiatry and Behavioral Sciences, University of Washington and Harborview Medical Center, Seattle.*

Reprint requests to: Deborah S. Cowley, M.D., Department of Psychiatry and Behavioral Sciences, Box 356560, University of Washington Medical Center, 1959 NE Pacific Street, Seattle, WA 98195.

Several effective treatments for panic disorder are now available. These include tricyclic antidepressants,[1] monoamine oxidase inhibitors (MAOIs),[2] benzodiazepines,[1,3] serotonin selective reuptake inhibitors (SSRIs),[4] and cognitive-behavioral therapy.[5] However, although these modalities yield response rates of 50%–90% in placebo-controlled clinical trials, a significant number of patients fail initial treatment and thus fall into a category anecdotally referred to as "treatment-resistant panic disorder."[6–9]

Patients treated in naturalistic settings fare worse, with "zero panic attack" rates of 30%–80% reported in studies following up patients after 1–8 years.[10] The majority of patients continue to suffer from chronic or recurring anxiety, panic, phobic avoidance, and functional impairment. The higher rates of "treatment resistance" or incomplete recovery in naturalistically treated samples are doubtless due to the highly selected nature of clinical trial participants, who are younger, healthier, more willing to withstand the rigors of a medication study, and less likely to have comorbid psychiatric disorders. Furthermore, cognitive-behavioral therapy remains unavailable to many patients with panic disorder.

Thus, poor response to initial pharmacologic treatment of panic disorder is a significant problem in naturalistic treatment settings. In spite of this, there are scant data available to shed light on the reasons for treatment failure or optimal therapeutic approaches to these patients. Several authors of review articles have used clinical experience to outline factors that may contribute to treatment failure.[6–9] These have included medical and psychiatric comorbidity; discontinuation of medication due to adverse side effects; and inadequate dose, duration, or frequency of administration of medication. Indeed, a number of reports suggest that only a minority of

patients with panic disorder receive optimal pharmacologic treatment.[11–14]

The aim of the present study was to identify more systematically the reasons for failure of prior naturalistic pharmacologic treatment in 106 consecutive patients with panic disorder referred to a specialty anxiety and mood disorders clinic. Specifically, we sought to determine the relative importance of clinician-related factors, such as choice of a medication ineffective for panic disorder and use of inadequate doses or duration of treatment, versus patient- or illness-related factors, such as intolerance of medication side effects and comorbid conditions. In those tolerating adequate medication trials, we aimed to determine the rate of true "treatment resistance," or failure to respond to an effective medication given at a therapeutic dose for an appropriate length of time. Finally, we wished to examine whether any demographic or clinical characteristics are associated with the patient-related phenomenon of medication intolerance or the illness-related phenomenon of true "treatment resistance." On the basis of prior long-term naturalistic outcome studies,[10] we hypothesized that failure to respond to adequate medication trials would be associated with patient characteristics of phobic avoidance and Axis I and II comorbidity.

METHOD

Subjects

Subjects were 106 consecutive patients with DSM-III-R panic disorder with or without agoraphobia who were evaluated between October 1986 and August 1990 by two psychiatrists (D.S.C., P.R.B.) at the Center for Anxiety and Depression at the University of Washington, Seattle. This fee-for-service clinic serves as a secondary referral source for expert evaluation and treatment services. Most patients are seen for consultation and then referred back to community practitioners with recommendations for future management.

Procedure

Data were generated as part of a standard initial assessment and subsequent follow-up study[15] and were based on a systematic patient interview that included information regarding age at onset of panic disorder, duration of illness, and total number of medications tried in the past. For each medication trial, the dose, frequency of administration, duration of treatment, side effects, compliance, response, and reason for discontinuation were recorded. Response was defined as the patient's subjective, retrospective assessment of whether the medication had been of benefit (complete or partial response) or not (minimal or no response). Reasons for discontinuation were classified as lack or loss of therapeutic benefit, dose-limiting side effects, concerns about dependency, pregnancy, or "other" (e.g., had recovered, did not want to take medication anymore). Other variables to be assessed were derived from an existing database collected during past studies using this patient population.[15–18] This database included Axis I and II diagnoses derived from administration of the Structured Clinical Interview for DSM-III-R, and scores on the Hamilton Rating Scale for Depression (HAM-D),[19] Hamilton Rating Scale for Anxiety (HAM-A),[20] Beck Depression Inventory (BDI),[21] and Revised Ways of Coping Checklist.[22]

Data Analysis

The adequacy of medication trials (effective medication, sufficient dose and duration) was assessed using criteria proposed by Yonkers et al.[14] In that report, a review of published literature was used to categorize medications as being effective or not and, for each effective medication, to specify low, standard, and high dosage ranges. For example, alprazolam is listed as an effective medication for which < 2.0 mg/day is a low dose, 2.0–8.0 mg daily is a standard dose, and > 8.0 mg daily is a high dose. Dose ranges for imipramine are < 150 mg (low), 150–300 mg (standard), and > 300 mg (high), while those for phenelzine are < 45 mg (low), 45–90 mg (standard), and > 90 mg (high). Data on established efficacy for SSRIs were added to the Yonkers criteria. For example, paroxetine was considered to have a standard dose of 20–60 mg daily. Medications prescribed at low doses or for inadequate durations according to Yonkers and colleagues' guidelines were considered inadequate medication trials. Ineffective medications included bupropion, buspirone, β-blockers, and antihistamines.

To examine possible determinants of medication intolerance and true treatment resistance, we compared demographic and clinical characteristics in those who discontinued one or more effective antipanic medications due to side effects (N = 38) versus those who did not (N = 53), and in those who failed an adequate medication trial (N = 13) versus those who responded (N = 30). Comparisons were performed using t tests for continuous and chi-square or Fisher's exact test for categorical variables. Stepwise logistic regression was then performed to determine the relative contributions of those variables that differed significantly between groups.

Table 1. Outcome of 190 Trials of Effective Antipanic Medication in 91 Patients

Reason for Discontinuation	Benzodiazepine Trials (N = 105)	Antidepressant Trials (N = 85)	Total (N = 190)
Still taking medication	54 (51%)	18 (21%)	72 (38%)
Intolerable side effects	7 (7%)	44 (52%)	51 (27%)
Lack/loss of benefit	26 (25%)	20 (24%)	46 (24%)
Other (improved, did not want to take medication)	9 (9%)	3 (4%)	12 (6%)
Concerns about dependency	8 (8%)	0 (0%)	8 (4%)
Pregnancy	1 (1%)	0 (0%)	1 (0.5%)

RESULTS

Sample Characteristics

Of 106 cases, 30 were men and 76 were women. Mean ± SD age at intake was 37.4 ± 12.0 years (range, 18–72). The mean age at onset of panic disorder was 29.0 ± 10.6 years (range, 8–62), while the mean duration of illness was 8.4 ± 9.6 years (range, 0.2–52). Forty (38%) had panic disorder alone and 66 (62%) had panic disorder with agoraphobia. Seventy percent had at least two Axis I diagnoses. The overall mean number of Axis I diagnoses was 2.4 ± 1.2 (range, 1–6). Of note, 54 (51%) reported current and 61 (58%) reported lifetime major depression. Forty percent of the sample had at least one comorbid Axis II diagnosis, with the overall mean number of Axis II diagnoses being 0.97 ± 1.5 (range, 0–6).

Use of Effective Medications and Adequate Medication Trials

Of the 106 patients, 8 had never taken antipanic medication, 5 had been prescribed p.r.n. benzodiazepines only, 17 had tried one medication, 20 had tried two, 12 had tried three, 13 had tried four, and 31 had tried five or more antipanic medications. Detailed information was available for a total of 252 medication trials.

Only 91 (86%) of 106 patients had been treated with at least one effective antipanic medication prescribed regularly, rather than on an as-needed basis. Forty-three of these 91 also received an adequate medication trial, while 48 did not. However, only 11 of the 48 reported obtaining no benefit from treatment. Thus, overall, 15 patients did not undergo any trial of regularly prescribed, effective antipanic medication, and 11 patients received inadequate medication trials, despite tolerating the medication and obtaining no therapeutic benefit from the dose prescribed.

Table 2. Demographic and Clinical Variables in Patients With and Without a History of Discontinuing a Medication Due to Side Effects (DSE)*

	nonDSE N = 53		DSE N = 38		Analysis		
Variable	N	%	N	%	χ^2	df	p
Female	34	64	31	82	3.29	1	.07
College degree	19	37	14	37	10.10	7	NS
Married	42	79	29	76	2.81	5	NS
Agoraphobia	35	66	26	68	0.06	1	NS
Depression							
Current	29	55	22	58	0.09	1	NS
Lifetime	33	62	24	63	0.01	1	NS
Substance abuse	19	36	6	16	4.47	1	.03
	Mean	SD	Mean	SD	t	df	p
Age (y)	36.2	9.3	42.5	13.3	1.78	32	.08
Age (y)	36.8	10.1	39.6	13.9	1.12	89	NS
Age at onset of panic disorder (y)	29.1	10.2	30.6	11.4	0.66	89	NS
Duration of panic disorder (y)	7.5	6.9	9.0	11.3	0.77	89	NS
# Axis I diagnoses	2.5	1.4	2.3	1.1	0.99	89	NS
# Axis II diagnoses	1.0	1.4	1.1	1.6	0.23	76	NS
Coping							
Avoidance	0.18	0.04	0.18	0.06	0.08	88	NS
Self-blame	0.20	0.07	0.18	0.09	0.87	88	NS
Problem-focused coping	0.19	0.05	0.19	0.07	0.20	88	NS
Seeks social support	0.22	0.07	0.23	0.08	0.57	88	NS
Wishful thinking	0.22	0.06	0.22	0.06	0.19	88	NS
HAM-A	21.9	7.9	27.1	11.3	2.38	74	.02
HAM-D	15.3	6.7	18.0	8.2	1.60	74	.11
BDI	15.8	9.0	18.9	11.8	1.37	85	NS

*Abbreviations: DSE = discontinued at least one medication due to side effects, nonDSE = no history of discontinuing medication due to side effects; BDI = Beck Depression Inventory; HAM-A = Hamilton Rating Scale for Anxiety; HAM-D = Hamilton Rating Scale for Depression.

Of all 252 medication trials in the whole patient group, only 190 (75%) used medications likely to be effective for panic disorder and prescribed regularly rather than only as needed. Of these 190 trials with effective medications, 105 used benzodiazepines, 66 were of tricyclic antidepressants, 12 used MAOIs, and 7 used SSRIs. Fifty-nine trials (23% of all medication trials) were adequate in dose and duration. Of the remaining 131 trials of effective antipanic medication, only 28 were rated by the patient as having been of no or minimal therapeutic benefit.

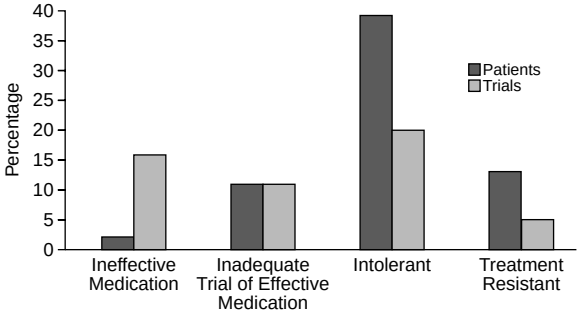
Reasons for Medication Discontinuation

Reasons given by patients for discontinuation of trials using effective medications are shown in Table 1. Of note, the most common reason for discontinuation was dose-limiting side effects in 51 trials (27% of all trials of effective medication and 43% of those trials of effective medication in which medication was then discontinued).

Table 3. Demographic and Clinical Variables in Patients Who Failed Versus Responded to an Adequate Medication Trial

	Failed N = 13		Responded N = 30		Analysis		
Variable	N	%	N	%	χ^2	df	p
Female	8	62	21	70	0.30	1	NS
College degree	3	23	9	31	4.04	7	NS
Married	10	77	23	77	4.30	4	NS
Agoraphobia	8	62	19	63	0.01	1	NS
Depression							
Current	10	77	16	53	2.11	1	NS
Lifetime	12	92	18	60	4.49	1	.03
Substance abuse	4	31	8	27	0.08	1	NS
	Mean	SD	Mean	SD	t	df	p
Age (y)	36.2	9.3	42.5	13.3	1.78	32	.08
Age at onset of panic disorder (y)	30.4	11.5	32.3	12.7	0.47	41	NS
Duration of panic disorder (y)	6.0	4.6	10.1	11.6	1.22	41	NS
# Axis I diagnoses	2.6	0.9	2.3	1.1	0.98	41	NS
# Axis II diagnoses	1.0	1.2	1.1	1.6	0.23	37	NS
Coping							
Avoidance	0.18	0.04	0.17	0.04	0.82	40	NS
Self-blame	0.18	0.12	0.18	0.09	0.08	40	NS
Problem-focused coping	0.20	0.06	0.18	0.06	0.93	40	NS
Seeks social support	0.22	0.08	0.24	0.08	0.67	40	NS
Wishful thinking	0.22	0.06	0.23	0.06	0.67	40	NS
HAM-A	25.2	7.6	24.1	11.3	0.32	34	NS
HAM-D	18.7	8.6	16.9	6.6	0.71	34	NS
BDI	15.8	12.0	18.3	9.7	1.71	40	NS

Figure 1. Overall Summary of Reasons for Treatment Failure*



*Percentage of patients shown is percentage of those tried on medication (N = 98) who failed treatment due to use of ineffective medications only, due to inadequate trials of effective medication (dose not limited by side effects), due to intolerable side effects, and due to failure to respond to an adequate medication trial (treatment resistant).

Percentage of medication trials is percentage of all 252 medication trials in 98 patients that failed due to use of ineffective medications, inadequate trials of effective antipanic medications, medication intolerance (side effects), and despite an adequate medication trial.

Clinical and demographic characteristics of those patients discontinuing at least one medication trial as a result of side effects (DSE group) and those who did not stop medication due to side effects (nonDSE group) are shown in Table 2. The DSE group had significantly higher HAM-A scores and was significantly less likely to have a history of substance abuse or dependence. There was a trend for the DSE group to contain a higher percentage of women. Based on stepwise logistic regression, the factors most significantly associated with medication intolerance were higher HAM-A scores ($p = .03$) and absence of substance abuse/dependence history ($p = .04$; model $\chi^2 = 10.3$, $df = 2$, $p = .006$).

To examine to what extent benzodiazepines were better tolerated than antidepressants, we also compared reasons for discontinuation in trials using these two classes of medication (see Table 1). Trials using benzodiazepines were significantly less likely to be discontinued due to side effects ($\chi^2 = 48.7$, $df = 1$, $p < .001$), were more likely to result in concerns about dependency ($\chi^2 = 6.84$, $df = 1$, $p < .01$), and were more likely to result in treatment continuation ($\chi^2 = 18.2$, $df = 1$, $p < .001$). Of note, although the numbers of trials using SSRIs and MAOIs were small (7 and 12, respectively), rates of discontinuation due to side effects were lower with these medications than with tricyclic antidepressants. Specifically, medication was discontinued due to side effects in 2 (29%) of 7 SSRI trials, 4 (33%) of 12 MAOI trials, and 38 (58%) of 66 tricyclic antidepressant trials.

True Treatment Resistance

Forty-three patients received a total of 59 adequate medication trials. As might be expected, adequate trials were more likely to result in therapeutic benefit, which was reported in 45 (76%) of 59 adequate trials as opposed to 61 (47%) of 131 other trials of effective antipanic medications.

Of the 43 patients receiving adequate medication trials, 30 (70%) responded to all adequate medication trials, while 13 (30%) failed one or more adequate trials. Demographic and clinical characteristics of these treatment-responsive versus treatment-resistant patients are shown in Table 3. The treatment-resistant group showed a significantly higher rate of lifetime major depression and a trend toward younger age. Based on stepwise logistic regression, both lifetime major depression ($p = .03$) and younger age ($p = .05$) remained significantly associated with treatment resistance (model $\chi^2 = 10.1$, $df = 2$, $p = .006$).

Summary of Reasons for Treatment Failure

An overall summary of reasons for pharmacologic treatment failure in this patient group and in all 252 medication trials is displayed in Figure 1. Of note, the most common reason for treatment failure, for both individual patients and specific medication trials, was intolerable side effects. Although 13% of patients failed at least one adequate medication trial, only 5% of all medication trials failed due to true treatment resistance.

DISCUSSION

To our knowledge, this is the first systematic, data-based study of reasons for failure of naturalistic pharmacologic treatment for panic disorder. The results confirm prior clinical impressions[6–9] that the major reasons for treatment failure are inadequate dose and duration of treatment, as well as medication intolerance. In fact, the most common reason for discontinuation of treatment in this study was medication side effects.

There are several obvious limitations of this study. First, this was a retrospective study relying on self-reported treatment histories of patients, rather than a prospective, controlled trial. However, this method provides a more inclusive and representative sample of patients seen in psychiatric practice. Secondly, the most commonly prescribed agents were benzodiazepines, followed by tricyclic antidepressants. These prescribing practices reflect the lack of knowledge about the antipanic efficacy of SSRIs until quite recently. SSRIs are now generally considered the first-line treatment for panic disorder[23,24] and typically result in fewer adverse effects than do tricyclics. Finally, the adequacy of medication trials remains difficult to determine, since dose requirements vary widely among individual patients. Use of standardized dosage ranges may have led to an underestimate of the number of "adequate" trials. The strengths of the current study include the use of structured interviews and standardized rating scales and the inclusion of a wide variety of patients treated naturalistically in the community.

Only a minority of patients in this study reported having been treated with an adequate trial of antipanic medication. This is consistent with prior reports demonstrating underutilization of effective treatments in panic disorder.[11–14] For example, Taylor et al.,[11] in a 1989 report, found that fewer than 15% of volunteers for a panic disorder study had received imipramine. Of 100 patients with panic disorder seen at a university anxiety disorders clinic, only 15% had been treated with imipramine, 13% with alprazolam, and 11% with cognitive-behavioral therapy.[12] Even among patients treated by psychiatrists in academic medical centers, only 54% of the most symptomatic patients had received optimal pharmacologic management.[14]

The use of ineffective or p.r.n. only medication in our own or other studies may have been a result of a lack of physician knowledge or of patient preference to avoid regularly prescribed medication. In our own patient group, a major reason for not achieving adequate doses or duration of treatment was discontinuation due to intolerable side effects. However, it is also noteworthy that almost 50% of inadequate trials resulted in therapeutic benefit. It is possible that the treating physician felt it unnecessary to increase the dose if the patient was reporting improvement. Without more detailed information regarding the extent of therapeutic benefit obtained, it is difficult to assess whether these patients were responding optimally at lower than the standard doses outlined by Yonkers et al.,[14] or whether, as may be more likely, patients were maintained at a dose producing some but not optimal improvement.

Intolerable side effects played a major role in treatment failure in the patients in our study. As expected, dose-limiting side effects were significantly more likely to lead to discontinuation of antidepressants than of benzodiazepines. Although this is consistent with results of clinical trials,[1,3] the magnitude of the difference is greater than would have been predicted. For example, in the Cross-National Collaborative Panic Study,[1] dropouts due to side effects were listed as being 3.4% for the alprazolam group and 5.9% for the imipramine group. Even if all 14.1% of imipramine-treated patients who "refused treatment" did so due to adverse effects, the total dropouts due to side effects from that study (20%) would still be far less than the dropout rate in our patient group. Overall tolerability of tricyclic antidepressants in clinical trials (total number of patients entered minus those dropping out for any reason) has ranged from 50%–80% with acute treatment[1,2,25–27] and 45%–58% after 1 year,[25,26] while tolerability of benzodiazepines has ranged from 75%–89% with acute treatment[1,26,27] and 70% after 1 year.[26] Once more, our results are consistent with this pattern, since in 51% of benzodiazepine but only 21% of antidepressant trials were patients still taking the medication. The higher side effect rates and lower tolerability of medications in our group may reflect slower dosage increases and more frequent monitoring in clinical trials or duration of treatment longer than 1 year in our group. However, it is more likely that unselected patients treated in the community include those more vulnerable to or less willing to endure unpleas-

ant side effects than those patients participating in clinical treatment studies.

It would be hoped that dropouts due to side effects will be lower and tolerability higher in community treatment settings with widespread use of SSRIs. Although only 7 of the 252 medication trials that we examined used SSRIs, the rate of discontinuation due to side effects was lower than that seen with tricyclic antidepressants. In a controlled trial of paroxetine,[4] the reported dropout rate due to side effects was 6%, and overall tolerability of SSRIs has ranged from 72%–85% acutely[4,28–31] and 70%–76% after 1 year.[30,31] These figures are similar to those obtained with benzodiazepines and superior to results with tricyclic antidepressants and provide reason for optimism, although it remains to be seen whether or not increased use of SSRIs to treat panic disorder in unselected community populations will markedly reduce the significance of medication intolerance as a determinant of treatment failure.

Treatment failure due to side effects was associated with patient characteristics of higher HAM-A scores and an absence of lifetime substance abuse/dependence. Higher levels of anxiety, reflected by higher HAM-A scores, may contribute to increased sensitivity to somatic symptoms, including adverse medication effects. Those patients with a history of substance abuse or dependence may be less sensitive to bodily changes, either as a preexisting characteristic allowing them to tolerate adverse effects of drugs and alcohol, or due to desensitization resulting from repeated episodes of intoxication and withdrawal.[32] Of note, alcoholics with panic attacks have less intense feelings of panic and fear associated with sodium lactate infusion than do non–substance abusing patients with panic disorder, despite reporting similar increases in physical symptoms of anxiety and panic.[32,33]

In the current study, treatment-resistant patients were more likely to report a lifetime history of major depression. This is consistent with some prior reports that patients with both panic disorder and major depression may have a worse prognosis than those with either disorder alone.[34] Our findings reinforce the importance of recognition and aggressive treatment of major depression in patients with panic disorder. Other comorbid conditions, including agoraphobia, Axis I and II disorders, and substance abuse, did not differ between treatment-resistant and treatment-responsive patients. However, the current sample of treatment-resistant patients was quite small, reducing our power to detect group differences. In addition, we were unable to assess a number of factors potentially associated with poor treatment response,[35,36] such as use of caffeine, alcohol, and over-the-counter medications; sleep deprivation; life events; or medical illness.

In summary, our results provide data supporting the clinical impression that patients with panic disorder often receive inadequate medication trials and discontinue medication due to intolerable side effects. A smaller proportion of patients seem to have true treatment resistance or failure to respond to adequate medication trials that are tolerated to completion. These findings are consistent with prior suggestions that only a small proportion of treatment-refractory depressed patients have true treatment resistance[37] and was true even in our group of patients referred to a specialty anxiety and mood disorders clinic.

Since most patients with panic disorder are treated initially in primary care settings, it is particularly important for psychiatrists to educate their primary care colleagues regarding which medications are effective for panic and the importance of adequate doses and duration of treatment. The importance of dose-limiting side effects may decrease with increased use of SSRIs. However, it is likely that we will need to develop more antipanic medications with less adverse side effects. Cognitive-behavioral therapy has been proved effective as a first-line treatment for panic disorder and to facilitate taper of benzodiazepines.[5,38] Increased availability of cognitive-behavioral therapy or development of cognitive-behavioral strategies specifically designed to increase tolerance of medication side effects would be valuable for medication-intolerant patients. Finally, prospective studies using adequate medication trials are necessary to further define the characteristics of patients likely to fail standard treatment for panic disorder.

Drug names: alprazolam (Xanax), bupropion (Wellbutrin), buspirone (BuSpar), imipramine (Tofranil and others), paroxetine (Paxil), phenelzine (Nardil).

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DISCLOSURE OF OFF-LABEL USAGE

The following agents mentioned in this article are *not* indicated for treatment of panic disorder: imipramine, MAO inhibitors, e.g., phenelzine.

Instructions

Psychiatrists may receive 1 hour of Category 1 credit toward the American Medical Association Physician's Recognition Award by reading the article starting on page 555 and correctly answering at least 70% of the questions in the quiz that follows.

1. Read each question carefully and circle the correct corresponding answer on the Registration form.
2. Type or print your full name, address, phone number, and fax number in the spaces provided.
3. Mail the Registration form along with a check, money order, or credit card payment in the amount of $20 to: Physicians Postgraduate Press, Office of CME, P.O. Box 752870, Memphis, TN 38175-2870.
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All replies and results are confidential. Answer sheets, once graded, will not be returned. Unanswered questions will be considered incorrect and so scored. Your exact score can be ascertained by comparing your answers with the correct answers to the quiz, which will be printed in the *Journal* issue after the submission deadline. The Physicians Postgraduate Press Office of Continuing Medical Education will keep only a record of participation, which indicates the completion of the activity and the designated number of Category 1 credit hours that have been awarded.

1. Effective medication treatments for panic disorder include all of the following *except:*
- a. Imipramine
- b. Bupropion
- c. Paroxetine
- d. Alprazolam
- e. Phenelzine

2. Based on the findings in this study, which would be the *most* important improvement in pharmacologic management of treatment-refractory panic disorder?
- a. Development of medications with greater efficacy
- b. Development of cheaper medications
- c. Development of medications with less risk of dependency
- d. Referral of all patients with panic disorder to psychiatrists
- e. Development of medications with less adverse side effects

3. The major reason for medication treatment failure in the patients reported in this article was:
- a. Side effects
- b. Use of ineffective medications
- c. Inadequate medication doses
- d. Inadequate duration of medication trials
- e. True treatment resistance

4. Currently, what class of medications is considered the first-line pharmacologic treatment for panic disorder?
- a. Tricyclic antidepressants
- b. Benzodiazepines
- c. Antihistamines
- d. Serotonin reuptake inhibitors
- e. MAO inhibitors

5. Prior studies have shown that:
- a. Effective antipanic treatments are widely used in the majority of patients with panic disorder
- b. More patients are treated with cognitive-behavioral therapy than with medication
- c. Overall tolerability of paroxetine is superior to that of tricyclic antidepressants
- d. Overall tolerability of tricyclic antidepressants is superior to that of benzodiazepines
- e. Patients with a history of substance abuse have better outcomes with medication

6. Naturalistically treated patients with panic disorder differ from patients treated in clinical trials in that they are:
- a. Younger
- b. Healthier
- c. More likely to have comorbid psychiatric disorders
- d. Carefully selected for treatment
- e. More likely to respond to cognitive-behavioral therapy

7. Compared with medication trials using tricyclic antidepressants, those using benzodiazepines were:
- a. Less likely to be discontinued due to side effects
- b. Less likely to be discontinued due to fears of dependency
- c. Less likely to have been continued
- d. All of the above
- e. None of the above

Answers to the June 1997 CME quiz

1. d
2. e
3. e

Circle the one correct answer for each question.

1.	a	b	c	d	e
2.	a	b	c	d	e
3.	a	b	c	d	e
4.	a	b	c	d	e
5.	a	b	c	d	e
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1. Overall quality of this CME activity ____
2. Content ____
3. Format ____
4. Faculty ____
5. Achievement of educational objectives:
   - A. Enabled the reader to identify currently available effective treatments for panic disorder. ____
   - B. Enabled the reader to appreciate the importance of choosing effective medication and using an appropriate dose and duration of treatment. ____
   - C. Enabled the reader to recognize that true treatment resistance is uncommon and that treatment failure is most often due to medication intolerance or inadequate medication trials. ____
6. This CME activity provided a balanced, scientifically rigorous presentation of therapeutic options related to the topic, without commercial bias. ____
7. Please comment on the impact that this CME activity might have on your management of patients.

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