Unemployment and Emergency Room Visits Predict Poor Treatment Outcome in Primary Care Panic Disorder

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Background: To complement existing data on predictors of treatment response in groups of "pure" panic disorder patients studied in clinical trials or in poorly controlled naturalistic follow-up, we sought to elucidate predictors of treatment response over 1 year in a diagnostically heterogeneous and comorbidly ill group of primary care patients with panic disorder participating in a randomized effectiveness study.

Method: Patients with DSM-IV panic disorder (N = 115), mostly without agoraphobia, were recruited from 3 primary care clinics in Seattle, Wash., and randomly assigned to an on-site collaborative care intervention (N = 57), in which psychiatrists provided education, 2 visits, follow-up phone calls, and paroxetine, or to usual care by their primary care physician (N = 58). Predictors of response at 3-month intervals over 1 year were determined using logistic regression analysis.

Results: Patients with consistent response over the year (response at the majority of available timepoints) were significantly ($p < .05$) more likely to be white, employed, in higher income strata, and in the intervention group and had less medical comorbidity and phobia severity, fewer recent hospitalizations and emergency room visits, and higher reported Medical Outcomes Study 36-Item Short Form physical and role functioning. The final regression model indicated that responders were more likely to be in the intervention group, be employed, and lack a recent emergency room visit.

Conclusion: While some of the univariate findings partially replicate previous results linking greater illness severity with poorer response, univariate findings linking medical comorbidity and low socioeconomic status with poor response, as well as multivariate findings that unemployment and recent emergency room use are the most potent predictors of poor response, have not been previously reported.

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As with most mood and anxiety disorders, only a proportion of patients with panic disorder respond to acute pharmacologic treatment. In clinical trials, approximately 60% to 70% of patients have a positive response to treatment, while only 30% to 40% experience complete remission.[1] A number of short-term medication studies covering periods less than a year have sought to identify potential predictors of response in patients with panic disorder. Studies have generally found that more severely ill patients, whether defined by longer duration of illness,[2] greater symptom severity,[3–5] comorbid depression,[3,6] comorbid agoraphobia,[4,5] other phobia,[4,7] or comorbid personality disorder,[8] respond less well. The results of longer-term, naturalistic studies covering periods from 1 to 5 years have generally found similar predictive power for the same variables, including duration of illness,[9] symptom severity,[10,11] comorbid depression,[10,11] phobia,[10,11] and personality disorder.[10,12] Although less definitive, studies of predictors of response to cognitive-behavioral therapy (CBT) for panic have also shown similar findings.[13,14]

While it is generally acknowledged that the majority of short-term studies have been clinical trials with their relatively homogeneous samples, artificially enforced treatment, and high attrition, many longer-term naturalistic studies have also selected patients after the completion of a clinical trial or from tertiary care research settings.[15] Virtually all studies, except for the large Harvard-Brown Anxiety study,[16] have included sample sizes under 100, and in short-term studies, attrition rate has been relatively high. The majority of longer-term naturalistic studies are

unable to collect accurate information about type and adequacy of treatment, and so this is rarely considered in predictive analyses. All studies have been conducted in specialty mental health settings, although many samples were recruited from the community. No studies have been completed on samples of panic disorder patients seen in the primary care medical setting, where the disorder is common; many of these patients tend to present complaining of the physical manifestations of their panic attacks,[17] and treatment can reduce unnecessary use of medical resources. These prior small, relatively homogenous samples may have limited the ability to detect certain predictors (e.g., unemployment, low income, ethnic minority status, pattern of health service use, medical comorbidity) because of the narrow range of variability in these studies. Finally, the majority of these studies have focused on response at a single, cross-sectional point in time, a possible limitation, since 1 study[13] has shown that cross-sectional and longitudinal responses in panic patients are poorly correlated.

As part of a 1-year randomized effectiveness trial of a collaborative care (CC) intervention for primary care panic disorder that compared psychiatrist-assisted pharmacotherapy and psychoeducation/disease management with usual care (e.g., pharmacotherapy) by the primary care physician,[18] we examined prediction of consistent response over time in a large heterogeneous group of 115 patients. CC patients showed greater improvement on anxiety, depression, and disability measures at 3 and 6 months, along with a greater likelihood of adequate pharmacotherapy. In this sample, the primary care context, the presence of a longer follow-up time, more medical, psychiatric, and substance use comorbidity than usually seen in clinical trials, a broader range of socioeconomic status and ethnicity, and an extremely low attrition rate (because all patients were assessed continually despite nonadherence, by telephone) provide a unique opportunity to analyze treatment predictors.

METHOD

Subjects

Settings for this study were 3 Seattle, Wash., primary care clinics: 2 university-associated internal medicine clinics and a community family medicine clinic. Patients had to be between 18 and 65 years of age and meet DSM-IV criteria for panic disorder, with at least 1 panic attack in the past month. We accepted all psychiatric and physical comorbidities except those that were potentially life threatening (e.g., active suicidal ideation or terminal medical illness) or those that would limit patient participation or adherence (psychosis, current substance abuse, dementia, and pregnancy). Patients had to be English-speaking and have a phone. We excluded patients currently receiving psychiatric treatment and patients currently receiving or applying for disability benefits. Although referrals from physicians were encouraged, we also recruited patients in the waiting room using a highly sensitive 2-question panic disorder screen.[19] All positive screens and referrals received a phone diagnostic interview to determine final eligibility. The study procedure was approved by the Institutional Review Board of the University of Washington School of Medicine, Seattle.

Patients were randomized by research assistants, using a random number table, either to the CC intervention (N = 57) or to usual primary care treatment (N = 58). Randomization was stratified by recruitment method (screen or referral)[20] and whether or not they had an additional comorbid Axis I diagnosis. As can be seen in Table l, these panic patients had Anxiety Sensitivity Inventory (ASI) and Panic Disorder Severity Scale (PDSS) scores comparable to those seen in panic patients in clinical settings, but lower phobia scores. After complete description of the study to the subjects, written informed consent was obtained.

Intervention Condition

A multifaceted intervention targeted patient, physician, and process-of-care variables. Patients were provided an initial psychiatric assessment, at which time they were prescribed the selective serotonin reuptake inhibitor paroxetine. On the day of randomization, CC patients were also mailed both a psychoeducational videotape about the nature and treatment of panic disorder[21] and an educational pamphlet about the medication and its side effects. Two follow-up psychiatric phone calls and a second visit were offered to adjust medications and address side effects or to further discuss clinical issues. Although no formal cognitive therapy was offered, patients were encouraged to expose themselves, as tolerated, to any feared and avoided situations after pharmacologic treatment had blocked panic attacks.

A schedule of extended care aimed to overcome the usual lack of planned follow-up and monitoring in acute care–oriented primary care[22] (1-hour psychiatric visit week 1; 10- to 15-minute telephone call week 2; 30-minute visit week 4; telephone call between weeks 6 and 8). Between months 3 and 12, psychiatrists attempted to telephone patients 5 times at equal intervals to reinforce the importance of medication adherence and address any other pertinent issues.

Usual Care Condition

"Usual care" (UC) patients received treatment as usual (i.e., pharmacotherapy) from their primary care physician in the clinic, who received the results of the initial diagnostic phone assessment to eliminate nonrecognition of panic and associated disorders as a factor in outcome. Specialty mental health referral was also permitted; approximately 20% of patients requested such a referral.

Table 1. Comparison of Treatment Nonresponders and Responders on Study Variables[a]

Variable	Nonresponders (N = 42)	Responders (N = 55)	Univariate Statistics[b]	Wald t (df = 1)
Demographics				
Men	11 (26)	23 (42)	1.91	1.54
White	23 (55)	43 (78)	4.98*	5.26*
Married	12 (29)	19 (35)	0.16	0.08
Unemployed	20 (48)	12 (22)	12.25** (df = 2)	11.94** (df = 2)
Income, $				
< 10,000	8 (19)	5 (9)		
10,000–20,000	12 (29)	6 (11)	13.09** (df = 3)	11.54** (df = 3)
20,000–35,000	16 (38)	19 (35)		
> 35,000	6 (14)	25 (46)		
Income < $20,000	20 (48)	11 (20)	7.13**	8.31**
Age, y, mean (SD)	42.3 (9.3)	39.4 (9.7)	1.45	0.64
Study characteristics				
Intervention	11 (26)	35 (64)	11.93***	NA
Adequate medication at least once	25 (60)	41 (74)	1.83	0.13
Psychiatric, substance, and medical comorbidities				
Agoraphobia	18 (43)	20 (36)	0.29	0.08
Social phobia	14 (33)	22 (40)	0.14	0.70
GAD	18 (43)	22 (40)	0.03	0.15
OCD	7 (17)	7 (13)	0.09	0.23
PTSD	10 (24)	7 (13)	1.46	0.85
Major depression	20 (48)	29 (53)	0.03	0.03
Alcohol-positive	10 (24)	14 (25)	0.01	0.01
Drug-positive	8 (19)	8 (15)	0.10	0.91
CIRS–medical comorbidity (range, 0–4),[c] mean (SD)	1.6 (0.5)	1.2 (0.6)	3.44***	7.32**
Clinical severity, maximum/minimum score				
ASI (0–64)	30.3/13.2	29.3/11.5	0.39	0.29
CES-D (0–60)	27.9/14.8	23.7/12.1	1.54	2.01
PDSS total (0–28)	12.4/6.6	12.7/5.0	0.23	0.01
Fear total (0–8)	3.0/1.4	2.2/1.4	2.74**	6.09**
Agoraphobia fear (0–8)	2.4/1.9	1.4/1.5	2.63**	4.24*
NEO (1–5)	2.6/0.9	2.8/0.7	0.92	0.82
Utilization in 3 months prior to baseline (except lifetime psychiatric inpatient)				
Any inpatient non-psychiatric stay	8 (19)	3 (5)	3.13	4.34*
Lifetime psychiatric inpatient stay	11 (26)	6 (11)	2.86	1.51
≥ 1 ER visit	20 (48)	7 (13)	12.75***	15.00***
Any outpatient psychiatry or psychology	10 (24)	8 (15)	0.81	2.41
No. of primary care visits, mean (SD)	4.5 (4.8)	4.4 (4.1)	0.04	0.06
Functioning (mean [SD] SF-36 score; 0–100 for all scales)[d]				
General health	49.6 (25.8)	55.1 (24.1)	1.08	1.20
Physical functioning	67.3 (28.8)	86.3 (20.4)	3.80***	9.70**
Mental health	50.8 (22.3)	50.5 (17.6)	0.08	0.05
Pain	35.3 (21.7)	35.8 (18.0)	0.11	0.01
Role-emotional	34.1 (38.6)	41.8 (41.7)	0.93	0.56
Role-physical	37.5 (44.6)	60.0 (41.3)	2.57**	5.54*
Role-overall	4.5 (2.4)	3.3 (2.3)	2.41*	4.79*
Social functioning	58.5 (29.5)	58.8 (30.8)	0.04	0.01
Vitality	31.9 (21.1)	37.8 (18.7)	1.46	2.61

[a]Values shown as N (%) unless otherwise noted.
[b]Chi-square tests with corrections for continuity for categorical data and t tests with df = 84 for continuous variables.
[c]A rating of 4 indicates most severe medical illness.
[d]An SF-36 rating of 100 indicates perfect health, and a rating of 0 indicates worst health.
*p < .05. **p < .01. ***p < .001.
Abbreviations: ASI = Anxiety Severity Inventory, CES-D = Center for Epidemiological Studies-Depression Scale, CIRS = Cumulative Illness Rating Scale, ER = emergency room, GAD = generalized anxiety disorder, NEO = Neuroticism-Extroversion-Obsessionality, OCD = obsessive-compulsive disorder, PDSS = Panic Disorder Severity Scale, PTSD = posttraumatic stress disorder, SF-36 = Medical Outcomes Study 36-Item Short Form.

Assessments

Patients were assessed at 3-month intervals by phone interviewers blind to randomization status. Interviewers based at each of the 3 clinics always assessed patients at a clinic other than their own. However, blindness was not validated by asking interviewers to guess the patient's treatment condition. The interview included portions of the Composite International Diagnostic Interview (CIDI),[23] modified for DSM-IV, which has acceptable reliability for mood and anxiety disorder diagnoses.[24–26] Telephone structured psychiatric interviews have high concordance with in-person interviews.[27–29] To screen for significant substance abuse, we asked simple questions about frequency of use of alcohol or illicit substances.

Use of more than 3 to 4 drinks daily or 6 drinks twice a month, use of marijuana more than once a week, or use of any other substance (e.g., cocaine, opiates, inhalants) more than once a month disqualified subjects from the study. The interview also included the PDSS,[29] a reliable and valid scale that rates a spectrum of panic disorder symptoms and is sensitive to treatment effects[30]; the ASI,[31] a core measure of panic disorder apprehension and discomfort about psychological and physical symptoms of anxiety that predicts risk for panic, maintenance of panic in the absence of treatment, and long-term outcome[32] and is under significant genetic control[33]; the Fear Questionnaire,[34] which measures phobic symptoms; the Centers for Epidemiologic Studies-Depression Scale (CES-D),[35] a reliable and valid measure of depression; the Medical Outcomes Study 36-Item Short Form (SF-36),[36] a widely used health status inventory; a single 1–5 Likert scale item from a previous study[33] that measured patient satisfaction with recent care for personal and emotional problems; the Neuroticism-Extroversion-Obsessionality (NEO) Neuroticism Scale,[37] which measures a neurotic "trait" that predicted poor outcome in previous CC studies[38]; and the Cumulative Illness Rating Scale (CIRS),[39] which uses medical chart review to measure degree of medical comorbidity.

Adequacy of antipanic medication (appropriate type, dose, and duration of 6 weeks) was rated from patient self-report during the assessments using a previously published algorithm based on a review of panic disorder efficacy studies.[40] We elected to use a threshold of 20 mg as an adequate dose for paroxetine because our CC protocol allowed psychiatrists to stop at 20 mg if patients had responded (consistent with recent data)[41] or had dose-limiting side effects.

Defining Response Groups

This was a year-long study in which data were assessed at 4 timepoints following baseline (3, 6, 9, and 12 months). Of the total sample, 6 patients (5%) did not complete any of the 4 follow-up assessments, and 12 patients (10%) only completed 1 of the 4 assessments. Since the goal of this study was to examine predictors of response over time, these patients were not used in the statistical analyses.

Percent change scores from baseline were calculated for the remaining 97 patients using the PDSS. Response was defined as in previous studies[18,29] as a 40% or greater decrease in PDSS total score. Fifty-five patients (57%) were classified as responders because they met criteria for response at a majority of available assessments (i.e., all 4 assessments, 3 of 4 assessments, or 2 of 2 assessments). Thirty patients (31%) were defined as nonresponders because they did not meet criteria for response at a majority of available assessments (i.e., all 4 assessments, 3 of 4 assessments, or 2 of 2 assessments). Twelve percent of the patients (N = 12) had half of their assessments indicate response and half indicate nonresponse. They were classified as nonresponders and used in the statistical analyses. Since these patients could have been also classified as responders, all the analyses were repeated with the 12 patients in the responder group. The results were virtually identical to those in which the patients were classified as nonresponders. The same predictors were found at the same significance level. For ease of presentation, the results are presented with the 12 patients in the nonresponder group.

Statistical Analyses

Patients included in the study were compared on all study variables with those who were not included (see Table 1) using chi-square tests with corrections for continuity for discrete data and t tests for continuous variables. Univariate statistics were then calculated comparing the responder and nonresponder groups based on the distributions of the variables. Logistic regression models were then used to determine the significance of the predictors.

Demographics (age, gender, race, marital status, employment, and income), psychiatric and medical comorbidity (psychiatric diagnoses and CIRS scores), illicit use of any substance other than marijuana (i.e., cocaine, amphetamines, opiates, ecstasy), baseline clinical severity (ASI, CES-D, PDSS, Fear Questionnaire [measuring total phobia and agoraphobia], and NEO scores), service utilization prior to baseline (psychiatric, primary care, and emergency room [ER]), and health status using the SF-36 scales were tested as potential predictors. Potential predictors were individually tested for significance using the Wald t statistic to determine their significance in the presence of treatment group status (UC or CC) to predict response group. Predictors that were significant in the logistic models at $p < .05$ were tested together using backward and forward stepping to arrive at a final logistic regression model (all variables, $p < .05$). No interactions of treatment group with the significant predictors were statistically significant. No statistical outliers were observed in either model. The odds ratios for the model terms and their 95% confidence intervals were calculated.

RESULTS

The 97 patients included in this study were compared with the 18 patients not included on all study variables included in Table 1. Patients not included in this study were more likely to be male (83%) than those who were included (35%) ($\chi^2 = 12.57$, df = 1, $p < .001$) and also had a significantly lower rate of an adequate panic medication trial (22%) than those who were either responders or nonresponders (68%) ($\chi^2 = 11.53$, df = 1, $p = .001$). Lastly, patients not included reported poorer physical functioning on the SF-36 (63.6 ± 26.8) than patients included in this study (78.0 ± 26.0) ($t = 2.15$, df = 113, $p = .03$).

Table 2. Model for Response

Variable	β	Wald t	df, p	Odds Ratio	Lower 95% CL	Upper 95% CL
Treatment group	2.39	14.44	1, <.001	10.95	3.19	29.78
At least 1 ER visit	–2.35	11.74	1, <.001	0.09	0.02	0.37
Employment	. . .	8.07	2, .018	. . .	. . .	. . .
Full time vs unemployed	1.63	7.58	1, .006	5.12	1.60	13.40
Full time vs part time	0.41	0.29	1, .59	1.51	0.34	6.78

Abbreviations: CL = confidence limit, ER = emergency room.

Using the PDSS 40% criterion (Table 1), in addition to assignment to the intervention, 11 variables were significantly related to a positive response: being white, being employed, an annual income greater than $20,000, lower medical comorbidity, lower total phobia and agoraphobia scale scores, a lower rate of medical inpatient hospitalizations, lower rates of a recent ER visit, better physical function, fewer physical role limitations, and fewer overall role limitations. The univariate and logistic regression results were very similar, indicating that controlling for intervention did not affect the differences between the response groups.

Table 2 illustrates the details of the final model predicting response. Two nontreatment variables predicted response: being employed and not visiting the ER in the last 3 months prior to study entry. The model was highly significant ($\chi^2 = 41.20$, df = 4, $p < .001$) and correctly classified 78% of patients (71% of the nonresponders and 84% of the responders).

In order to further understand why visiting the ER may be a prognostic indicator of poor response, we performed chart reviews to identify reasons for ER visits and post hoc analyses between those patients who did and did not visit the ER in the 3 months prior to baseline, regardless of response grouping. Seventy-nine patients did not visit the ER, and 36 patients had at least 1 ER visit. Chart review indicated that the majority (21/36, 58%) of patients with ER visits were evaluated for documented complications of medical illness and no anxiety symptoms were noted in the chart (although anxiety still could have prompted an emergency visit). Only 6 (17%) of the 36 remaining patients had no medical reasons listed in the chart to explain their somatic symptoms (e.g., chest pain, dizziness), whereas in the other 9 (25%), ER evaluation noted evidence for both medical illness–related complaints as well as symptoms of anxiety. The entire subgroup with visits at baseline did not have significantly higher ASI scores (t = 1.40, df = 113, p = NS), although they did have significantly higher PDSS scores (t = 3.83, df = 113, p = .0001), suggesting that anxiety most likely played some role in their ER presentation.

Consistent with this finding, those with at least 1 ER visit, in comparison with patients with no ER visits, were more likely to be older, be non-white, have lower income levels, and have been a medical inpatient, and were more medically ill, with poorer physical, role, and social functioning. In addition, those with at least 1 ER visit reported higher levels of depression and more panic symptoms at baseline.

DISCUSSION

In this analysis of the longer-term response of a broader sample of panic patients treated in a medical setting, a larger number of response predictors emerged, compared with previous cross-sectional studies examining this issue mostly in specialty settings. Several of the predictors are consistent with previous findings[2–14] that suggest that patients with more severe forms of panic disorder are less responsive. In particular, more severe agoraphobia and overall phobia and more role function impairment predicted poor response, although neither severity of panic at baseline using both the ASI and PDSS nor presence or severity of comorbid depression was a predictor. The expected low rate of agoraphobia in this primary care sample also may have limited panic severity analysis. We did not have a measure of overall duration of illness for this analysis.

Other variables also emerged as important predictors of nonresponse, including lower socioeconomic status (measures of employment, income, and ethnicity), greater severity of medical illness/poor physical condition, and more frequent medical service use, both hospitalizations and ER visits. A number of studies have linked low socioeconomic status to an increased prevalence of various psychiatric disorders, especially depression,[42,43] but also panic disorder,[44,45] as well as a poorer prognosis[42,46,47] and more chronicity.[48] No studies, however, have examined the association of socioeconomic status with prognosis or outcome in any of the anxiety disorders. It is likely that unsafe neighborhoods, greater exposure to trauma,[49] more chronic social stressors such as unemployment, poor housing, lack of transportation and child care, and less overall ability to control one's life[50,51] all contribute to the association of low socioeconomic status with poor outcome. It is also possible that unemployment may be a proxy for longer duration of more severe panic disorder.

A number of studies have documented that chronic medical illness is associated with increased prevalence and poorer outcome in depressive disorder.[52,53] While no studies have examined this issue in anxiety disorders, numerous medical illnesses commonly co-occur in patients

with panic disorder and may mimic the symptoms of panic and make assessment and treatment more difficult.[17]

Finally, another unique predictive variable was a history of visiting the ER in the past 3 months. Our chart review indicated that most of these visits were for medical illness rather than somatic presentations of panic and so are unlikely to just reflect severity of panic disorder. However, residual anxiety might prompt patients with medical problems to present emergently to an ER rather than wait for a day or 2 to visit their primary care physician. Furthermore, these visits could also reflect the likelihood that patients with low socioeconomic status more often utilize the ER as a regular source of care, being less likely to have a primary care physician (however, all of these patients were recruited in the primary care setting and so had been receiving care there). We had no data on the timing or urgency of these visits that might clarify these possibilities.

The most powerful predictor of response was assignment to the intervention. Although the intervention was designed to optimize pharmacotherapy prescription and adherence, it also included psychoeducational and social support elements, which obviously were important. These findings contrast with those of virtually all longer-term naturalistic studies, which have shown that treatment was either unrelated to outcome[10,12] or related to poorer outcome.[9,13] In these naturalistic analyses, treatment was never carefully measured, so quality of treatment could not be assessed. Furthermore, because more severely and persistently ill patients tend to receive more treatments over time in an attempt to improve their condition, a paradoxical association of treatment with poorer outcome in some patients often will counterbalance and cancel out any treatment association with good outcome.

In conclusion, this analysis demonstrates that a wider range of variables is predictive of panic disorder treatment outcome when a heterogeneous primary care patient population is examined. While some predictors were conceptually consistent with findings from previous studies (i.e., overall severity of illness predicts poor outcome), others have not been previously noted. Moreover, the most powerful predictors of poor response, unemployment and recent ER visits, have not been shown to be predictive of response in studies of panic patients seen in specialty medical health settings. Because medical illness and, to a lesser degree, somatization contributed to ER visits, this suggests that the competing priorities of ruling out serious acute medical illness and caring for chronic medical illness may limit accurate diagnosis and effective treatment of primary care panic. On a more practical note, these 2 simply ascertained measures (unemployment and ER visits) could be easily used to identify panic patients at high risk for nonresponse to routine intervention so that more potent treatment regimens (e.g., adjunctive pharmacotherapy or combination treatment with medication and CBT) could be pursued in a timelier manner.

Drug name: paroxetine (Paxil).

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