Clinical Significance of Lifetime Panic Spectrum Symptoms in the Treatment of Patients With Bipolar I Disorder

Ellen Frank, PhD; Jill M. Cyranowski, PhD; Paola Rucci, DStat; M. Katherine Shear, MD; Andrea Fagiolini, MD; Michael E. Thase, MD; Giovanni B. Cassano, MD, FRCPsych; Victoria J. Grochocinski, PhD; Bryan Kostelnik, BA; David J. Kupfer, MD

Background: Given the observed association between panic disorder and bipolar disorder and the potential negative influence of panic symptoms on the course of bipolar illness, we were interested in the effects of what we have defined as “panic spectrum” conditions on the clinical course and treatment outcome in patients with bipolar I (BPI) disorder. We hypothesized that lifetime panic spectrum features would be associated with higher levels of suicidal ideation and a poorer response to acute treatment of the index mood episode in this patient population.

Methods: A sample of 66 patients with BPI disorder completed a self-report measure of lifetime panic-agoraphobic spectrum symptoms. Patients falling above and below a predefined clinical threshold for panic spectrum were compared for clinical characteristics, the presence of suicidal ideation during acute treatment, and acute treatment response.

Results: Half of this outpatient sample reported panic spectrum features above the predefined threshold. These lifetime features were associated with more prior depressive episodes, higher levels of depressive symptoms, and greater suicidal ideation during the acute-treatment phase. Patients with BPI disorder who reported high lifetime panic-agoraphobic spectrum symptom scores took 27 weeks longer than those who reported low scores to remit with acute treatment (44 vs 17 weeks, respectively).

Conclusions: The presence of lifetime panic spectrum symptoms in this sample of patients with BPI disorder was associated with greater levels of depression, more suicidal ideation, and a marked (6-month) delay in time to remission with acute treatment. Alternate treatment strategies are needed for patients with BPI disorder who endorse lifetime panic spectrum features.

Arch Gen Psychiatry. 2002;59:905-911

From the Department of Psychiatry, Western Psychiatric Institute and Clinic (Drs Frank, Cyranowski, Rucci, Shear, Fagiolini, Thase, Grochocinski, and Kupfer), and the Department of Psychology (Dr Frank and Mr Kostelnik), University of Pittsburgh, Pittsburgh, Pa; and the Departments of Psychiatry, Neurobiology, Pharmacology, and Biotechnology, University of Pisa, Pisa, Italy (Drs Rucci and Cassano).

©2002 American Medical Association. All rights reserved.
Previous analyses had pointed to an association between medical record–reviewed anxiety symptoms and treatment outcome among our patients with BPI disorder.21 Given the evidence from UP depression research,2,6,8 our own examination of panic spectrum symptoms in UP depression,9 and the earlier medical record–review results,21 we expected that patients with BP disorder endorsing higher scores on a comprehensive panic-agoraphobic spectrum assessment11 would display higher levels of suicidal ideation and a poorer response to treatment than patients without such panic spectrum features. The current report examines the occurrence and clinical significance of lifetime panic spectrum symptoms among patients with BPI disorder treated in an outpatient psychiatric clinic.

PA TIENTS AND METHODS

PATIENTS

The study group consisted of 66 patients participating in a larger randomized, controlled trial (MH129618, E.F., principal investigator),23 36 of whom were included in our earlier report on the influence of medical record–reviewed anxiety symptoms on treatment outcome among individuals with BPI disorder.21 Patients in the larger treatment trial were recruited via medical referrals, referrals from inpatient mood disorder units and outpatient clinics at the Western Psychiatric Institute and Clinic, Pittsburgh, Pa, and media announcements. Of the 66 patients included in the current study, 23 (34.8%) were recruited from inpatient units, while 43 (65.2%) were recruited from outpatient sources. Treatment outcome data reported herein are drawn from the acute (or preliminary) treatment phase of the protocol. Data on panic spectrum symptoms are drawn from a single cross-sectional assessment that occurred when patients were at various points in this long-term protocol. In most cases (92%), this assessment followed completion of the acute treatment phase or termination from the study protocol.

To be enrolled in the larger protocol, patients were required to be between the ages of 18 and 65 years, to meet Research Diagnostic Criteria4 for BPI or schizoaffective manic disorder, and to be in an acute affective episode. The index episode had to meet severity criteria (ie, a Hamilton Depression Rating Scale [HDRS] score of ≥15 or a Bech-Rafaelsen Mania Scale score of ≥15). Exclusion criteria included the following: pregnancy, current rapid cycling (≥4 affective episodes per year), lifetime diagnosis of schizophrenia or antisocial personality disorder, current drug or alcohol abuse (unless confined to affective episodes), and significant medical illness that would preclude protocol pharmacotherapy.

TREATMENT PROTOCOL

After giving written, informed consent, participants were randomly assigned to the acute-treatment phase consisting of algorithm-based pharmacotherapy accompanied by either intensive clinical management or interpersonal and social rhythm therapy (IPSRT).23 Protocol pharmacotherapy began with the administration of lithium carbonate and ultimate stabilization receiving lithium monotherapy was encouraged. Patients who could not tolerate lithium therapy received either divalproex sodium or carbamazepine, or a combination of mood stabilizers. Patients with depression who failed to stabilize while receiving a mood stabilizer alone received either tranylcypromine sulfate or, if they were unwilling to take a monoamine oxidase inhibitor, paroxetine or another antidepressant in addition to their mood stabilizer. Neuroleptics were given as adjunctive medication to patients with manic, mixed, or psychotic symptoms who could not be stabilized using a mood stabilizer alone.

Intensive clinical management has been described as a nonspecific low-dose therapy aimed at providing education and support, reviewing symptoms, reinforcing medication adherence, and assisting patients in the management of any adverse effects of the medications. In contrast, IPSRT is a procedurally specified psychotherapy that focuses on problems in interpersonal relationships, the link between mood and life events, the importance of maintaining regular daily routines, and the identification and management of potential precipitants of rhythm dysregulation.24 Both clinical management and IPSRT were provided in the format of weekly individual sessions, both subject groups were treated according to identical pharmacotherapy guidelines, and in both conditions patients met with their therapist and psychiatrist at each visit. Because preliminary analyses on 124 patients randomly assigned to these 2 treatment conditions showed no difference in either the percentage of patients who remit with treatment or time to remission,21 treatment group is not controlled for statistically in subsequent analyses.

ASSESSMENTS

Clinical History and Status

Both current status and lifetime history of DSM-IV diagnoses were assessed via Structured Clinical Interview for the DSM-IV Axis I Disorders (SCID)16 performed at study enrollment by SCID-trained clinical evaluators (master’s- or doctoral-level nurses, social workers, or clinical psychologists). Following stabilization of the index episode, National Institute of Mental Health Life Charting Interviews17,18 were performed to supplement patient medical records and SCID interview data, and to obtain a more comprehensive account of patients’ lifetime mood episode history.

Throughout treatment, patients were assessed by independent clinical evaluators at each weekly clinic visit. Depressive symptoms were rated on both the 17-item and 25-item versions of the HDRS.20,30 Manic symptoms were assessed with the 12-item Bech-Rafaelsen Mania Scale.31 Full clinical remission is defined by an average 17-item HDRS score of 7 or less and an average Bech-Rafaelsen Mania Scale score of 7 or less over a period of 4 consecutive weeks. For the present analyses, time to remission was defined as the number of weeks from the first treatment session to the onset of this 4-week period of stabilization.

Panic-Agoraphobic Spectrum

The lifetime experience of panic-agoraphobic spectrum symptoms was assessed in a cross-sectional sample of 66 patients using the Panic-Agoraphobic Spectrum–Self-Report (PAS-SR). The term “panic-agoraphobic spectrum”17,18 refers to a broad array of features associated with DSM-IV panic disorder, including typical and atypical manifestations of core panic symptoms (such as paniclike somatic symptoms, anxious...
Table 1. Example Items From the Panic-Agoraphobic Spectrum Scale–Self-Report (PAS-SR)*

<table>
<thead>
<tr>
<th>Domain</th>
<th>No. of Items</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paniclike symptoms</td>
<td>27</td>
<td>Have you ever felt nervous, uncomfortable, or as though you were suffocating, because of a hot room, stale air, humid air, perfume, or other smells, even if the smells weren’t that strong?</td>
</tr>
<tr>
<td>Anxious expectation</td>
<td>5</td>
<td>At any time during your life have you ever worried a lot that there might be something terribly wrong that you cannot define, some type of nameless dread, something that you would be powerless to defend yourself from?</td>
</tr>
<tr>
<td>Agoraphobia</td>
<td>25</td>
<td>At any time during your life did you ever avoid, or fell nervous or uncomfortable wearing seat belts because you felt trapped?</td>
</tr>
<tr>
<td>Separation sensitivity</td>
<td>15</td>
<td>Did you ever have trouble going to sleep without someone nearby, or trouble sleeping away from home?</td>
</tr>
<tr>
<td>Stress sensitivity</td>
<td>2</td>
<td>At any time during your life have you ever noticed that the above [paniclike] symptoms come on very easily when you’re in a stressful situation, even when it was not that severe (eg, overworking, family problems, disruption of sleep or routine)?</td>
</tr>
<tr>
<td>Substance/medication sensitivity</td>
<td>9</td>
<td>Do you read the package insert more carefully than most other people because of feeling nervous or uncomfortable about taking medication?</td>
</tr>
<tr>
<td>Illness-related phobia and hypochondriasis</td>
<td>5</td>
<td>At any time during your life did you ever worry about reading medical articles or hearing someone talk about medical topics?</td>
</tr>
<tr>
<td>Reassurance sensitivity</td>
<td>26</td>
<td>Have you ever had your pulse or blood pressure checked repeatedly, even though your doctor didn’t recommend it?</td>
</tr>
</tbody>
</table>

*The total number of items in the PAS-SR is 114. Responses to PAS-SR items are scored as 0 (no) or 1 (yes). Responses are summed to obtain total PAS-SR scores that may range from 0 to 114.

expectation, and agoraphobia), as well as a range of related temperamental or behavioral features (categorized as separateness, anxiety, stress sensitivity, medication sensitivity, illness-related phobias, and reassurance seeking). The PAS-SR, a 114-item self-report scale, assesses the lifetime experience of panic-agoraphobic symptoms and features across 8 specified domains (Table 1).

The interview version of this measure has been shown to have excellent psychometric properties, and the 8 panic-agoraphobic spectrum subscales have been shown to display a strong pattern of convergent and discriminant validity with existing panic and anxiety assessment measures across multiple diagnostic groups and control subjects who were never psychiatrically ill. The self-report version of this instrument has been shown to agree very well (intraclass correlation coefficient = 0.94) with the interview version. Data obtained from a subset of 23 patients in the current sample indicated excellent test-retest reliability for the PAS-SR instrument over a 2- to 3-month period (Spearman ρ = 0.92, P < .001) (range, 50-91 days; mean [SD], 80.8 [9.5] days). In receiver operating characteristic curve analyses reported previously, a cutoff score of 35 was determined to best distinguish between psychiatric outpatients with and without clinically significant lifetime panic spectrum features.

STATISTICAL ANALYSES

High (≥35) and low (<35) PAS-SR scorers were compared across demographic and clinical characteristics using χ² and t tests. Yates correction was applied to χ² tests in 2 × 2 tables, and the Mann-Whitney test was used in place of t tests when the distribution of data was significantly skewed. When an association between categorical variables and PAS-SR scores was hypothesized a priori, we reported the odds ratios. Finally, for a subset of 45 patients on whom life chart data were available, associations between total PAS-SR scores and lifetime days depressed, manic, and “ill” (either depressed or manic) were assessed using the Pearson product-moment correlation coefficients.

Kaplan-Meier survival analyses were conducted to compare the median time to remission between patients above and below the cutoff for panic-agoraphobic spectrum. Dropouts were treated as censored data. Given our previous finding that patients treated for BP depression and mixed-cycling profiles take longer to achieve remission than those treated for manic episodes, a Cox proportional hazards regression model was used to examine the association between PAS-SR scores and time to stabilization, adjusted for the predominant mood state being treated. Similarly, to check whether the association between time to stabilization and PAS-SR score was related to a longer duration of illness, we used a Cox regression model with total PAS-SR score and time spent depressed or manic as independent variables. All tests were 2-tailed, and an α level of .05 was used to determine statistical significance.

CHARACTERISTICS OF PARTICIPANTS

An cross-sectional sample of 76 patients who had completed or nearly completed the acute-treatment phase of the protocol described earlier were invited to complete PAS-SRs. Of the 76 patients approached, 66 returned completed questionnaires for a response rate of 86.8%. Nonrespondents did not differ from respondents for age, sex, baseline psychiatric severity, or time to remission. Of the 66 respondents, 37 were female and 29 were male. Mean (SD) age of patients was 35.1 (11.0) years (range, 18-61 years). During the acute treatment phase, 33 of the patients were predominantly treated for depression, 21 for mania, and 12 for mixed-cycling episodes.

Using the PAS-SR cutoff score of 35, 33 (50%) were categorized as low PAS-SR scorers and 33 (50%) were categorized as high PAS-SR scorers. The median PAS-SR score among the low group was 19 (mean [SD], 17.97 [9.0]; range, 1-34), while the median PAS-SR score among the high PAS-SR group was 52 (mean [SD], 51.45 [13.4]; range, 35-87). Only 8 patients
(12.1%) reported a lifetime history of DSM-IV panic disorder. All of these patients had PAS-SR scores above the threshold of 35.

**DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF HIGH VS LOW PAS-SR SCORERS**

Patients with high PAS-SR scores were significantly more likely to be female and to report more lifetime depressive episodes and greater depressive symptoms at baseline (Table 2). Life charting data available for a subset of 45 patients indicated a significant correlation between higher PAS-SR scores and a greater number of lifetime days depressed ($r = 0.39$, $P = .01$) and lifetime days ill (ie, depressed or manic; $r = 0.36$, $P = .02$); however, the correlation between PAS-SR scores and lifetime days manic did not reach significance ($r = 0.23$, $P = .14$). Finally, patients with high PAS-SR scores were significantly more likely to have been treated for an affective episode that included depressive components (ie, BP depression or mixed-cycling presentations) during the acute treatment phase of the protocol ($60\%$ vs $28.6\%$, $t^2 = 4.5$, $P = .03$).

**DEPRESSIVE SYMPTOMS AND SUICIDALITY**

To examine the relationship between lifetime panic spectrum symptoms and the affective presentation of these patients, we compared weekly HDRS scores averaged across the acute treatment phase. As expected, high PAS-SR scorers reported higher levels of depression than low PAS-SR scorers (Table 3).

This finding may have been influenced by 2 potential confounds. First, high PAS-SR scorers were more likely to have been treated for depressed or mixed-cycling pre-
sentations (rather than pure mania) during the acute treatment phase. However, a 2-way analysis of variance (ANOVA) including both the PAS-SR group and the predominant state treated indicated that a high PAS-SR score was significantly associated with higher mean HDRS scores even after controlling for the predominant mood state treated (Table 3). A second potential confound was that a larger proportion of female patients were categorized as high PAS-SR scorers. Given the robust sex difference in life-time rates of depressive episodes among men and women with BP disorder, sex (rather than panic spectrum symptoms per se) could have accounted for this difference in depression scores. However, a 2-way ANOVA including both the PAS-SR group and sex indicated that a high PAS-SR score was significantly associated with higher mean HDRS scores even after controlling for sex (Table 3).

As predicted, high PAS-SR scorers were significantly more likely than low PAS-SR scorers to report suicidal ideation. Reports of suicidal ideation were derived from clinician ratings on item 3 of weekly HDRS evaluations. Any rating of suicidal ideation of 2 to 4 (ie, from mild to severe) obtained during the acute treatment phase was scored as a positive indication of suicidal ideation. Reports of suicidal ideation were derived from clinician ratings on item 3 of weekly HDRS evaluations.

To examine the effect of PAS-SR scores on time to remission within the depressed and mixed-cycling groups only (ie, excluding manic subjects, who tended to show lower PAS-SR scores and a quicker time to remission), a subsequent Kaplan-Meier survival analysis was conducted for this subgroup (n=45). This analysis indicated that high PAS-SR scorers still took significantly longer to remit (32.8 and 32 weeks, respectively) than patients treated for mania (13 weeks; Breslow test=16.5, df=2, P<.001).

As hypothesized, high PAS-SR scores were associated with a significantly longer median time to remission (44 weeks vs 17.1 weeks for patients with low PAS-SR scores) in a Kaplan-Meier survival analysis (Breslow test=13.6, degrees of freedom [df]=1, P<.001; Figure 1). A separate Kaplan-Meier survival analysis indicated that patients treated for mixed-cycling and depressive presentations also took significantly longer to remit (32.8 and 32 weeks, respectively) than patients treated for mania (13 weeks; Breslow test=16.5, df=2, P<.001).

TREATMENT RESPONSE

In line with these findings, a Cox regression model including dichotomous (high vs low) PAS-SR scores and predominant state treated as covariates was found to fit the data significantly better than the baseline model with no covariates (overall χ²=22.5, P<.001). This model indicated that high PAS-SR scores and having a depressed clinical presentation as the predominant state treated were significantly and independently associated with a longer time to remission (for PAS-SR score, risk ratio [RR]=0.33, df=1, P=.003; for depressive vs manic state, RR=0.39, df=1, P=.05; for mixed-cycling vs manic state, RR=0.44, df=1, P=.06).

In contrast, a Cox regression model including the total PAS-SR score, lifetime days depressed, and lifetime...
The prevalence of clinically significant panic-agoraphobic spectrum features in this sample of patients with BP disorder exceeds that observed in a previous report on patients with UP disorder assessed with the PAS-SR instrument.9 This is consistent with epidemiologic findings of Chen and Dilsaver13 and clinical findings of Pini et al.14 More important, the prevalence of these panic spectrum features was more than 4 times as great as that of lifetime panic disorder in these patients. Clinically significant lifetime panic spectrum was associated with female sex, higher levels of depression, a greater risk of suicidality, and a much longer time to remission of the index mood episode in this sample. These effects could not be explained by the increased likelihood of high PAS-SR scorers to be treated for depressed or mixed-cycling states15 rather than pure mania (that was associated with lower HDRS scores and the lowest rates of suicidal ideation). Analyses restricted to only those patients treated for depressed or mixed-cycling episodes showed that high PAS-SR scorers were still nearly 4 times more likely than low PAS-SR scorers to report suicidal ideation during the acute treatment phase and took more than 5 months longer than low PAS-SR scorers to remit from the acute mood episode (time to remission, 10.5 months vs 5.3 months, respectively). These findings highlight the crucial importance of assessing a broader range of panic features than those represented by the DSM-IV criteria for panic disorder and of monitoring suicidal symptoms in patients with BP disorder who present with depressed or mixed symptom profiles complicated by panic spectrum features.

For the current report, an empirically defined cut-off was used to distinguish between high and low PAS-SR scorers. The spectrum approach, however, was developed to provide a more dimensional assessment of underlying symptom constellations. Although a score of 35 may be a useful clinical indicator, continuous PAS-SR scores should provide more sensitive information to the clinician and the researcher. Indeed, continuous PAS-SR scores powerfully predicted time to remission in the current sample (using a Cox regression model, odds ratio, 0.96; 95% confidence interval, 0.93-0.99; P=.001).

Although Parker et al.15 postulated that symptoms of anxious (UP) depression were likely rooted in temperament, they noted the difficulty of identifying definitional markers encompassing not only symptoms but also related personality patterns and temperamental features. Such difficulties highlight the advantages of the spectrum approach. Categorical classification of panic disorder often fails to capture the broad array of atypical symptoms and related, yet enduring, temperamental features that can be associated with this core condition. In contrast, the PAS-SR casts a “wide net” to capture the lifetime experience of both classic panic symptoms as well as related, yet subtle, manifestations of this core condition. Moreover, the PAS-SR approach allows for the assessment of panic-related personality features without necessitating the clinical diagnosis of DSM-IV personality disorder. This may be advantageous, given the contention of Akiskal,30 Savino et al.,32 and others that the affective instability and common anxiety-mood comorbidities of patients with BP disorder are often misdiagnosed as Axis II personality disorders, such as borderline personality disorder. Perhaps the strongest evidence for the clinical usefulness of the PAS-SR assessment approach is evident in our treatment outcome findings. From the outset of our efforts to create structured assessments for spectrum disorders we have argued that such assessment could be useful in predicting clinical course and treatment decision making.

The current study is limited by the cross-sectional nature of the PAS-SR assessments; however, patients with high and low scores on the PAS-SR did not differ with regard to their current status in the study. In addition, our analytic approach was limited by the small sample size (n=66). Future studies with larger sample sizes may be able to examine the potential mechanisms by which lifetime panic-agoraphobic symptoms complicate the treatment of acute symptoms. Indeed, given existing theories regarding the role of temperamental factors and anxiety comorbidity in BP II disorder,32 future research on the prevalence and significance of panic spectrum features in patients with BP II disorder would be informative.

Our present findings, nevertheless, point to the clinical validity and potential usefulness of panic spectrum assessment in the management and treatment of patients with BP disorder, and highlight the need for development of alternate treatment strategies for these particularly challenging patients.

Submitted for publication December 13, 2000; final revision received September 26, 2001; accepted October 2, 2001.

This study was supported in part by the Bosin Memorial Fund of The Pittsburgh Foundation and by grants MH29618 (Dr Frank), MH30915 (Dr Kupfer), and training grant MH60473 (Dr Cyranowski) from the National Institute of Mental Health, Rockville, Md, and grants from Pfizer USA, New York, NY (Drs Frank and Shear).

This study was presented in part at the Fifth Annual Conference of Societa Italiana di Psicopatologia, Rome, Italy, February 25, 2000.

Reprints: Ellen Frank, PhD, Western Psychiatric Institute and Clinic, 3811 O’Hara St, Pittsburgh, PA 15213 (e-mail: franke@msx.upmc.edu).

REFERENCES


