Prodromal and Residual Symptoms in Bipolar I Disorder

Gabor I. Keitner, David A. Solomon, Christine E. Ryan, Ivan W. Miller, Alan Mallinger, David J. Kupfer, and Ellen Frank

The objective of the current study was to better understand the nature of prodromal and residual symptoms of mania and depression, as reported by patients with bipolar I disorder and their family members. Prodromal and residual symptoms of mania and depression were elicited from 74 patients with bipolar I disorder. In 45 cases, an adult family member provided similar information. Three clinicians classified the symptoms into six broad categories: behavioral, cognitive, mood, neurovegetative, social, and other. The clinicians also categorized symptoms as typical or idiosyncratic. Seventy-eight percent of the patients reported prodromal depressive symptoms and 87% reported prodromal manic symptoms; greater than half of the patients disclosed residual symptoms of depression (54%) and mania (68%). Within each of these four illness categories, cognitive symptoms were consistently the most common symptoms reported by patients. A substantial number of symptoms were idiosyncratic, particularly those reported for residual depression. Agreement between patient and family members on reported symptoms was strong for the prodromal phase of both polarities, but less so for the residual phases. These preliminary results suggest that patients with bipolar I disorder and their family members can identify prodromal and residual symptoms, that these symptoms are quite common, and that prodromal symptoms may be more prevalent or easier to identify than residual symptoms. Cognitive symptoms were consistently the most common symptoms reported by patients.

PATIENTS WITH bipolar I disorder require continuation and maintenance treatment to prevent relapses and recurrences. One means of improving this treatment is to better understand the natural history of the illness, including the onset and offset of mood episodes. In particular, greater knowledge about prodromal and residual symptoms would permit earlier recognition of incipient episodes and focus increased attention on episodes that have not fully remitted.

Kraepelin[1] identified prodromal symptoms in his classic description of manic-depressive illness, stating that "... patients themselves feel the approach of a fresh attack sometimes days or even weeks beforehand." Clinicians have attempted to detect these early signs to gain greater therapeutic control and to prevent recurrences,[2] and there is evidence that patients who are able to recognize and respond to early symptoms are significantly less likely to require hospitalization.[3] Prodromal symptoms may also distinguish different subtypes of bipolar I disorder; one study reported that subjects with rapid onset of mood episodes had a significantly longer duration of illness and a greater number of past mood episodes.[4] Residual symptoms warrant concern as they may engender considerable distress and disability that is not readily apparent to clinicians.[5]

Only a few efforts have been made to characterize systematically the phenomenology of prodromal symptoms in patients with bipolar I disorder, and even less has been done with regard to residual symptoms. One study prospectively assessed subjects for prodromal symptoms over a 9-month period using the Brief Psychiatric Rating Scale,[6] and found significant elevations in unusual thought content 1 month before manic relapses, and significantly higher levels of conceptual disorganization during the 4 months preceding depressive relapses.[7] A study investigating the relationship between life events and the onset of mania noted that the most common initial symptoms were increased activity, reduced sleep, and elated mood.[8]

Other studies of prodromal symptoms have been retrospective. An early study delineated three stages of mania, and classified symptoms as affective, cognitive, or behavioral.[9] The initial phase was observed in all study patients and was characterized by euphoric and labile mood,

From the Department of Psychiatry and Human Behavior, Brown University, Providence, RI; and the Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA.

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Address reprint requests to Gabor I. Keitner, M.D., Director, Mood Disorders Program, Department of Psychiatry, Rhode Island Hospital, 593 Eddy St, Providence, RI 02903.

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expansiveness, and increased activity. Another retrospective study found considerable intersubject variability in the specific symptoms constituting manic and depressive prodromes[10]; however, within each subject the symptoms were consistent in successive episodes of the same type. The most frequently reported symptoms in manic prodromes were increased activity, decreased need for sleep, and elevated mood. The most frequently cited symptoms in depressive prodromes were depressed mood, loss of energy, impaired concentration, and morbid thoughts. A third study categorized prodromal symptoms as behavioral, psychological, or idiosyncratic.[11] A manic prodrome was identified by 75% of the subjects and a depressive prodrome by 85%. The most frequently cited symptom during the manic prodrome was elevated mood. The most frequently cited symptoms during the depressive prodrome were anergia, decreased self-confidence, and social isolation. The majority of subjects identified idiosyncratic symptoms as part of their prodromes and reported consistency in the symptoms comprising prodromes of the same polarity.

In an effort to better understand the onset and offset of mood episodes in bipolar I disorder, a preliminary study was conducted examining symptoms of the four illness categories of prodromal and residual mania, and prodromal and residual depression. The present study extends previous work in this area by including residual symptoms—a phenomenon that has been virtually ignored. In addition, this study elicited reports from family members as well as patients, thereby providing another perspective to corroborate responses from patients.

METHOD

This study was conducted at two university-affiliated psychiatric hospitals (Brown University and University of Pittsburgh). Outpatients with bipolar I disorder were recruited from a variety of settings, including a psychopharmacology clinic for patients with mood disorders, a treatment study using psychotherapy and standard medical management, and a psychopharmacology treatment study. Diagnoses were made by the treating psychiatrist according to the criteria of DSM-III-R,[12] and in many cases, were confirmed with the Structured Clinical Interview for DSM-III-R.[13]

Subjects were given an open-ended self-report form, on which they recorded specific prodromal symptoms for previous episode(s) of mania and major depression. The form was worded as follows: "Please describe the behaviors you have experienced leading up to a manic or depressive episode. How can you tell that an episode is coming on?" A separate form was used to elicit residual symptoms of mania and major depressive disorder, and was worded as follows: "Please describe any mood, thought, feeling, etc. that persists or lingers even when it appears to others that the episode is over. What is still not right?" In addition, an adult family member was asked to record specific prodromal and residual symptoms from the patient's previous episode(s), using self-report forms nearly identical to those completed by the patient. Informed consent was obtained from each subject.

Two psychiatrists and a psychiatric nurse, working independently, classified each response within one of six broad domains: mood, behavior, cognition, neurovegetative, social, or other (Table 1). The "mood" category of included symptoms related to emotional state and affect. "Behavior" included symptoms related to activities, whereas "cognition" included symptoms related to thought processes such as memory and concentration. "Neurovegetative symptoms" were those associated with energy level, appetite, and sexual drive. The "social" category included symptoms primarily related to interpersonal interactions. Any symptom not fitting these five categories was relegated to the "other" category; examples included "less perceptive" and "dry skin." All disagreements in rating were resolved by consensus. In addition, the psychiatrists classified each symptom as typical (specified in DSM-III-R or in standard mood scales) or as idiosyncratic (novel symptom).

RESULTS

Of the 74 patients, 39 (53%) were women. The mean age was 42 (SD, ±12) years, and the mean education was 14 (SD, ±3) years. Marital status was as follows: 28 (41%) were married, 20 (29%) were single, 17 (25%) were divorced, two (3%) were widowed, two (3%) were cohabitating, and five (6.8%) did not provide this information.

In 45 cases, an adult family member also provided information on patient symptomatology. Table 2 shows that most patients and family members were able to identify some prodromal and residual symptoms.

Patients and family members reported a combined total of 1,284 symptoms. Of this total, 40% (516) were symptoms of prodromal mania, 16% (202) were symptoms of residual mania, 30% (387) were symptoms of prodromal depression, and 14% (179) were symptoms of residual depression.

Table 3 shows the proportion of patients reporting a particular type of symptom for each illness category. In all four categories, more

Table 1. Examples of Common Prodromal and Residual Symptoms in Bipolar Disorder

Category	Prodromal Symptoms		Residual Symptoms	
	Patient	Family	Patient	Family
Depression				
Behavioral	Quiet, withdrawn	Quiet	Slowed down	Puts things off
	Self-neglect	Less responsible	Late for work	Talks negatively
Cognitive	Poor concentration	Worried	Fear of relapse	Low motivation
	Can't make decisions	Down on self	Low self esteem	Low self-confidence
Mood	Crying	Sad	Irritability	Fear
	Irritable and angry	Irritable	Anxiety	Anxiety
Neurobehavioral	Poor sleep	Sleeps more	Low energy	Sleeps more
	Loss of appetite and energy	Low energy		
Social	Withdrawal from friends	Less affectionate	Distant from others	Unsociable
Mania				
Behavioral	More talkative	Talk too much	Still overactive	Restless
	More aggressive	Spends money	More subdued	Agitation
Cognitive	Increased confidence	More religious	Guilt	Self-absorbed
	Can't concentrate	Suspicious	Fear of relapse	Insecure
Mood	Feeling high	Elevated mood	Sadness	Sadness
	Irritability	Irritable	Worry	Loneliness
Neurobehavioral	Decreased sleep	Less sleep	Sleep problems	Sleep problems
	More energy	Poor appetite		High energy
Social	Talking more to others	Fights with family	Alienation	Isolation

patients reported cognitive symptoms than any other type of symptom.

The classification of the prodromal and residual symptoms reported by patients is shown in Table 4. Prodromal symptoms outnumbered residual symptoms. Cognitive symptoms were consistently the most common type of symptom reported. Neurovegetative symptoms were the second most common in the prodromal phase of both mania and depression, and mood symptoms were the second most common in the residual phases. Social and other symptoms were elicited least often.

The classification of prodromal and residual symptoms reported by family members is shown in Table 5. Again, prodromal symptoms outnumbered residual symptoms. Cognitive symptoms were cited most frequently in each of the illness categories, except in the instance of prodromal mania. During the residual phases of both mania and depression, behavioral symptoms were the second most common. Social and other symptoms were cited least often.

Symptoms were also classified dichotomously, depending on whether they were typical or idiosyncratic. Patients reported that idiosyncratic symptoms composed 45% of their symptoms of residual depression, 34% of their symptoms of prodromal depression, 24% of their symptoms of residual mania, and 15% of their symptoms of prodromal mania. Family members reported that idiosyncratic symptoms composed 32% of the symptoms of residual depression, 28% of the symptoms of prodromal depression, 23% of the symptoms of residual mania, and 21% of the symptoms of prodromal mania.

As stated above, 74 patients were studied, and in 45 cases an adult family member also provided responses. For each of these 45 pairs,

Table 2. Percent of Patients and Family Members Reporting Any Prodromal and Residual Symptoms

Category	Patients (N = 74)	Family Members (N = 45)
Prodromal mania	87	93
Residual mania	68	73
Prodromal depression	78	80
Residual depression	54	62

Table 3. Percent of Patients Reporting Any Symptoms by Illness Category (N = 74)

Symptom	Prodromal Mania	Residual Mania	Prodromal Depression	Residual Depression
Cognitive	57	42	45	38
Mood	39	36	42	19
Behavioral	47	18	20	9
Neurovegatative	47	8	39	18
Social	5	1	15	8
Other	16	8	19	4

Table 4. Classification of All Prodromal and Residual Symptoms Reported by Patients

Symptom	Prodromal Mania (N = 282) (%)	Residual Mania (N = 132) (%)	Prodromal Depression (N = 243) (%)	Residual Depression (N = 119) (%)
Cognitive	35	47	31	48
Mood	15	27	20	23
Behavioral	22	15	10	8
Neurovegetative	22	5	23	13
Social	1	1	7	7
Other	5	5	9	3

NOTE. N = Total number of symptoms. Percents do not add to 100 because of rounding.

the patient and corresponding family member were compared with regard to number of symptoms reported. Patients reported a greater number of symptoms than their corresponding family member in each of the four illness categories.

The reports were then compared to examine how often a patient and family member agreed on one or more specific symptoms. Of the patient/family member pairs who reported symptoms of prodromal mania, 64% of the dyads reported at least one identical symptom. For residual mania, only 28% of the dyads showed any agreement. In the case of prodromal depression, 59% of the pairs listed at least one identical symptom, whereas residual depression produced agreement in only 28% of the pairs.

DISCUSSION

Previous studies have found prodromal symptoms to be highly prevalent for both mania and depression, and the present study replicated this finding. In addition, more than half of the patients in this study experienced both manic and depressive residual symptoms. Patients and family members reported more prodromal symptoms than residual symptoms. Nearly 90% of patients and family members noted at least one prodromal symptom of mania, and about 80% noted at least one prodromal symptom of depression. Agreement on specific symptoms between patients and family members occurred more often for prodromal symptoms than for residual symptoms. A substantial number of the prodromal and residual symptoms were idiosyncratic.

Table 5. Classification of All Prodromal and Residual Symptoms Reported by Family Members

Symptom	% Prodromal Mania (N = 234)	% Residual Mania (N = 70)	% Prodromal Depression (N = 144)	% Residual Depression (N = 60)
Cognitive	18	34	33	38
Mood	17	23	18	13
Behavioral	47	26	13	18
Neurovegetative	13	7	27	17
Social	4	1	5	10
Other	2	9	3	3

The most common type of symptoms in this study were cognitive. This is inconsistent with previous studies of prodromal mania that most often found increased activity[8-10] and reduced sleep.[8,10] On the other hand, cognitive symptoms were commonly reported in prior studies of the prodromal depressive phase, as manifested by impaired concentration,[10] morbid thoughts,[10] decreased self-confidence,[11] and thought disorder.[7]

It is important to note that each of the various studies has used a different method to elicit responses. Some of the previous studies used structured questionnaires, and these may have shaped or limited responses. The present study used open-ended questions, so as not to restrict responses in any manner, and to determine whether patients could report and differentiate symptoms in different phases of the illness.

Limitations of the current study are that it was retrospective, that data were collected through self-reports, and that the clinical condition of the patients was not systematically evaluated at the time they completed the questionnaire. The clinical history (number of mood episodes, number of hospitalizations) was also not collected uniformly for each subject. Furthermore, the study did not gather information on the prevalence of mixed-prodromal or mixed-residual states—that is, the concomitant occurrence of subclinical manic and depressive symptoms. Nor was there any data to distinguish whether patients suffered episodic symptoms with long symptom-free intervals, or whether they cycled between subclinical mania and depression with continuous symptoms. Finally, no data was collected to investigate the presence of markers for seasonal exacerbations or other regularly occurring high-risk periods.

The high prevalence of prodromal and residual symptoms suggests that periodic prospective screening is feasible. Conceivably, such

screening could be used to direct treatment in such a way as to reduce the number of relapses, recurrences, and hospitalizations. An indication of this can be found in a treatment study that looked at the effect of lithium serum levels on subsyndromal symptoms and course of illness. Subsyndromal symptoms impose significant morbidity that falls short of meeting full criteria for a mood episode, and, in many cases, these subclinical symptoms are prodromal and progress directly to a mood episode. Following the onset of subsyndromal symptoms, patients with standard serum levels of lithium were less likely to relapse than were patients with low serum levels of lithium.[14]

Previous studies have overlooked the phenomenon of residual symptoms. The present study found residual mania in 68% to 73% of the cases and residual depression in 54% to 62% of the cases. These figures speak to the importance of maintenance therapy and long-term clinical monitoring, even if patients appear recompensated on the surface, as they represent high rates of clinical symptomatology.

The notion has been put forward that maintenance medication can be eliminated by monitoring patients for prodromal symptoms.[15] In one case report, two bipolar I patients were followed in this fashion over a 2-year period with good results.[16] However, in another series, five patients were followed in a similar manner for an average of 2 years.[17] During this time, three patients had recurrences and one patient experienced significant symptoms. Although certain patients may be able to forego maintenance medication through monitoring of prodromal symptoms, such a treatment plan should be approached cautiously as it is clear that most patients do poorly when pharmacotherapy is discontinued.[18] Indeed, there is substantial evidence that many bipolar I patients do poorly despite maintenance pharmacotherapy.[19-21] Thus, it seems that a better strategy is to further investigate the utility of monitoring prodromal symptoms as a means of optimizing maintenance treatment.

Toward this end, the information that was collected in this study will be used to develop a semi-structured questionnaire to assess both common and idiosyncratic prodromal and residual symptoms in a manner that addresses the limitations of the present study. It is important that this questionnaire be clinically relevant, easy to use, and that it readily tap into prodromal and residual symptoms as an aid to the long-term treatment of this recurring and remitting disorder. Through such efforts, patients, family members, and clinicians may learn more about the course of illness and how to better monitor patients so as to intervene in a timely fashion and, perhaps, prevent the most serious consequences of what are often socially disabling episodes.

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