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Detection of prodromal symptoms of relapse in mania & unipolar depression by relatives & patients

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***Background & objectives*: Detection of prodromal symptoms among patients with mania by their immediate relatives has been seldom examined. We carried out this study to examine the ability to detect and report prodromol symptoms of manic relapses by patients themselves and their relatives.**

***Methods*: The ability of patients and their relatives to detect prodromal symptoms was examined among 60 remitted patients, 30 each with DSM-IV diagnoses of bipolar disorder and recurrent depressive disorder, with recent manic/depressive relapses, and their 60 immediate relatives, using an instrument composed of items from common symptom-scales, as well as by unstructured interview.**

***Results*: Seventy per cent of patients with mania reported prodromes prior to relapse. This was significantly (P<0.01) less than the proportion of their relatives (97%), as well as the proportion of patients with unipolar depression (93%), reporting prodromal symptoms (P<0.05) among patients. Mean duration of the prodromal period reported by patients with mania was about 20 days (median-10 days); relatives reported durations which were longer by about 5 days. Prodromes of unipolar depression (mean 42.7 days; median- 21 days), were significantly longer than of mania, when reported by patients, but not by their relatives. Differences in reporting of prodromes, between relatives and patients seen in mania, were not observed in unipolar depression. The number and type of prodromal symptoms of mania reported was similar among patients and relatives.**

***Interpretation & conclusions*: Our findings showed that relatives of patients with mania were better at detecting prodromes of relapse; thus, input from relatives can improve the early detection of prodromal symptoms to prevent relapses of bipolar disorder.**

Key words Mania - patients - prodromes - relatives - unipolar depression

Bipolar affective disorder is a relatively common, severe and frequently disabling illness. It has a relapsing course with high risk of self-harm and suicide, and a high social burden[1, 2]. There is now a growing recognition of the importance of psychosocial determinants of bipolar disorder. Consequently, though medications remain the mainstay of treatment, several adjunctive psychosocial interventions have been developed for effective management of bipolar disorder. They have been shown to offer fairly consistent benefits to patients with bipolar disorder in preventing relapses and improving their functioning[2-4]. These interventions strategically target a number of critical domains such as medication compliance, symptom-recognition, residual affective

symptoms, and psychosocial functioning. Identification of early symptoms, which allows for early intervention and reduces several adverse consequences of a full-blown episode, is an important component of these treatments.

Prodromes are defined as the early signs and symptoms that herald a full-blown illness. Bipolar prodromes are any cognitive, behavioural and affective signs or symptoms that signal an oncoming episode[5]. The prodromal period generally refers to the time interval between the onset of the first prodromal symptom and onset of the characteristic signs/symptoms of the fully developed illness[6]. Prodromal symptoms are thus often used pragmatically as a short-hand for the early warnings that patients have of an impending episode[7].

Early identification of prodromal symptoms, whether used as a sole strategy[8], or as a part of more elaborate psychosocial interventions[9,10], has proved particularly beneficial in delaying relapses of bipolar disorder. This technique is based on clinical and research evidence, which indicates that most patients with bipolar disorder are able to successfully identify prodromal symptoms preceding manic, and to a lesser extent, depressive relapses[7,11,12]. Moreover, the length of the prodromal period is often sufficiently long to allow proactive help-seeking. Studies of typical prodromal symptoms have also revealed that a number of these symptoms occur in a social context, involving friends and families[13]. Accordingly, nearly all psychosocial treatments for bipolar disorder have stressed the importance of involving family members in identification and monitoring of prodromal symptoms[13,14]. However, despite this emphasis on the role of family members in detecting prodromal symptoms, very few studies have actually examined the ability of relatives to detect prodromal symptoms among patients with bipolar disorder[12]. Therefore, the current study was undertaken to examine the ability to detect prodromes, and reporting of prodromal symptoms of manic relapses, by patients with bipolar disorder, compared with their immediate relatives. Similar comparisons were also carried out in a group of subjects with unipolar depression, which served as a control condition.

Material & Methods

Selection criteria: patients and relatives: Consecutive patients with bipolar affective disorder with a manic relapse, or recurrent unipolar depressive disorder with a depressive relapse attending the psychiatry OPD of the Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, during the period from January to December 2005, were identified and screened. To be included in the study, patients had to fulfil DSM-IV criteria[15] for either of these two disorders, based on a structured interview. Patients also had to be in remission at intake, *i.e*. they had to have scores of <6 on the Young Mania Rating Scale[16], and scores of <7 on the Hamilton Depression Rating Scale[17]. Patients meeting other selection criteria, but not in remission, were inducted only after they had attained remission. Only adult patients (18-60 yr) and those accompanied by relatives were considered for inclusion. Patients in their first episodes, or those with co-morbid psychiatric disorders, or major physical disorders were excluded. Relatives included were healthy adults, living with the patient for a minimum of 2 years prior to inclusion, and intimately involved in the patient's care.

The study protocol was approved by the Research and the Ethics Committees of the institute. Written informed consent was obtained from all participants; other ethical safeguards were maintained during the conduct of the study[18].

Assessments: Diagnosis: Diagnoses were established using the Structured Clinical Interview for DSM-IV Axis-I Disorders, Clinician Version[19]. All assessments for prodromal symptoms were carried out within 2 wk of remission, or earlier. These were carried out by a single rater to obviate the need for determination of inter-rater reliability.

Detection of prodromal symptoms by patients and relatives: Information from patients, relatives and medical records was used to ascertain the onset of first prodromal symptom, as well as the onset of the full-blown episode. Patients and relatives were asked about any symptoms antedating the onset of the full-blown episode by six months or less, which were regarded as prodromal symptoms of the illness episode. Patients and relatives were also asked about premorbid traits and residual symptoms, to distinguish these from prodromal symptoms. All information was cross-checked from records, wherever available; any discrepancies were resolved by additional interviews. The time (in days) between the onset of first prodromal symptom and the onset of the full-blown episode was regarded as the duration of the prodrome.

Reporting of prodromal symptoms by patients and relatives: This was primarily assessed using an instrument specifically designed for this study. This

consisted of items derived from the Comprehensive Psychopathology Rating Scale[20], the Young Mania Rating Scale[16], the Bech-Rafaelsen Mania Rating Scale[21], the Beck Depression Inventory[22], and the Paykel's Clinical Interview for Depression[23]. Common prodromal symptoms reported in earlier studies of affective disorders were also included. All overlapping items were deleted. A brief description of each item was prepared. Items were rated as either present (1), or absent (0). The eventual scale consisted of 83 items. In addition, an unstructured interview was also conducted with patients and relatives to gather information about prodromal symptoms not included in this scale.

Statistical analysis: The Statistical Package for Social Scientists (SPSS), version twelve (SPSS Inc., Chicago IL, USA) was used for analysis. Frequencies, percentages, means, medians, standard deviations and range of observations were used for descriptive analysis. As all socio-demographic and clinical variables were normally distributed, these were compared between the two groups using the *t* test for continuous variables and the χ^2 test for categorical variables. Since the duration of prodromes was not normally distributed, the Mann-Whitney test was used to compare different groups. Moreover, because of the large number of tests of association carried out, results regarding prodromal symptoms have been reported both with and without the use of the Bonferroni correction for multiple comparisons.

Results

A total of 140 patients, 60 with mania and 80 with unipolar depression, were screened over a one-year period. However, only 60 patients (and their relatives), 30 each with mania or unipolar depression, were found suitable for inclusion. Those excluded had unclear diagnoses (n=15), co-morbidity (n=10), incomplete remission (n=14), refusal of consent (n=5), incomplete assessments (n=25) and lack of relatives (n=11). Although the final sample was less than half of the total patients screened, comparison of clinical and socio-demographic parameters between patients screened, and those eventually included, indicated that the final sample was representative of all patients screened.

Demographic and clinical profile: Patients in both groups were in their 30s; however, those with mania were significantly ($P<0.05$) younger than those with depression. Relatives were older, either parents or spouses of patients, and more likely than them to be better educated and working. Compared to patients of depression, those with mania had a significantly ($P<0.001$) lower age of onset, a longer duration of illness, significantly more ($P<0.01$) number of depressive episodes, a higher proportion with psychotic symptoms, and a higher proportion of those hospitalized for mania (Table I). Less than a-third of the patients with mania were on mood stabilisers, and less than half of the patients with unipolar depression were on antidepressants, prior to relapse. However, almost all patients were on medications by the time of induction.

Detection and reporting of prodromes by patients and their relatives: Seventy per cent of patients with mania could identify a definite prodrome prior to their relapse. This was significantly ($P<0.05$) less than the proportion of patients with unipolar depression (93%), who could detect prodromal symptoms. However, this difference was no longer significant after applying the Bonferroni correction. The proportion of immediate relatives (97%), who could detect a prodrome among patients with mania, was significantly ($P<0.01$) higher than the patients themselves (even after Bonferroni correction). In contrast, there were no significant differences between the proportion of patients with depression and their relatives who could identify prodromes among patients, or between relatives of both patient groups (Table II).

Mean duration of the prodromal period reported by patients with mania was 19.8 ± 24.8 days, with a median of 10 (range 2 to 105) days. Both the mean and median durations reported by patients with mania were significantly ($P<0.01$) less (even after Bonferroni correction), than those reported by patients with unipolar depression (mean 42.7±38.1; median 21; range 1-150 days). Though relatives of patients with mania reported mean and median durations which were longer by about 5 days, than those reported by the patients themselves, these differences were not significant. Contrastingly, relatives of patients with unipolar depressions reported a mean duration that was about 8 days less than the patients themselves; again, the difference was not significant (Table II).

Only the 21 most common prodromal symptoms among patients of both groups, reported by at least a-third of the patients and their relatives, have been highlighted (Table III). In both groups there were only minor and non-significant differences between patients and their relatives with regard to the number and type of prodromal symptoms reported, which did not conform to any pattern. Hence, combined

Table I. Demographics and clinical characteristics of patients

	Mania (BD) N=30	Depression (RDD) N=30
Age (yr)	33.8±9.1*	39.0±9.3
Male	21 (70)	17 (57)
Female	9	13
Single	11	5
Married	19 (63)	25 (83)
Employed	13	16 (53)
Unemployed	17 (57)	14
Schooling		
<10 yr	7	11
>10 yr	23 (77)	19 (63)
Family income		
< ₹3000/month	7	9
> ₹3000/month	23 (77)	21 (70)
Family type		
Nuclear	13	12
Non-nuclear	17 (57)	18 (60)
Residence		
Urban	16 (53)	18 (60)
Rural	14	12
Age of onset of illness (yr)	23.2±7.1***	31.5±8.3
Duration of illness (yr)	10.7±8.6	7.1±4.9
No. of manic episodes	5.3±4.19	-
No. of depressive episodes	1.1±2.5**	3.1±2.4
Duration of treatment (yr)	3.4±5.7	2.2±3.3
No. of hospitalizations	0.46 (0.77)	@
Average duration of hospitalization in months	0.65 (0.93)	@
Mood stabilizer prior to relapse	9 (30%)	-
Antidepressant prior to relapse	-	14 (47)
Current treatment after relapse		
Mood stabilizer	28 (93%)	-
Antipsychotics	2	-
Antidepressants	-	30 (100)
YMRS score	3.1±1.8	-
HDRS score	-	3.2±2.0

BD, bipolar affective disorder; RDD, recurrent unipolar disorder; @, only 1 patient hospitalized; YMRS, Young Mania Rating Scale; HDRS, Hamilton Depression Rating Scale
P *<0.05, **<0.01, ***<0.001 mania compared to depression
Values are mean ±SD. Values in parentheses are percentages

results for both patients and their relatives have been depicted (Table III). Among patients with mania 52 different symptoms were reported by both patients and relatives; 42 different symptoms were reported in depression by patients and relatives. Thirty symptoms were common to both patient groups. After applying the Bonferroni correction for multiple comparisons, hostility ($P<0.001$), ideas of grandiosity ($P<0.001$), distractibility ($P<0.001$), being uncooperative ($P<0.001$), and ideas of persecution ($P<0.001$), were reported significantly more frequently among patients with mania, whereas, sadness ($P<0.01$), worrying over trifles ($P<0.001$), talking less ($P<0.001$), lassitude ($P<0.001$), autonomic disturbances ($P<0.001$), indecision ($P<0.001$), reduced appetite ($P<0.001$), slowness of movement ($P<0.001$), not feeling like seeing people ($P<0.001$), and decreased sexual interest ($P<0.001$), were reported significantly more commonly among patients with unipolar depression.

Table II. Identification and duration of prodromes by relatives versus

Proportion of subjects who reported prodromal symptoms		
	Mania	Unipolar depression
Patients (n=30)	21 (70%)	28 (93%)[a]
Relatives (n=30)	29 (97%)[b]	27 (90%)
Duration (Days) of prodomal period as reported by the subjects		
Patients (n=30)	Mean±SD 19.8±24.8 Median - 10 Range - 2-105	Mean±SD 42.7±38.1[c] Median - 21[d] Range - 1-150
Relatives (n=30)	Mean±SD -25±28.3 Median - 15 Range - 2-120	Mean±SD -35.5±34.4 Median - 21 Range - 1-150

P values were also adjusted for multiple comparisons by using the Bonferroni correction; significance was set at 5% ($P = 0.05$); Bonferroni corrected *P* ($P = 0.05$/number of comparisons): 0.05/6 = 0.008. [a], Significantly more patients with unipolar depression reported prodromes - $X^2 = 5.61$; $P = 0.021$ (no longer significant after Bonferroni correction); [b], Significantly more relatives of patients with mania reported prodromes -$X^2 = 7.68$; $P = 0.006$ (significant even after Bonferroni correction). [c], Mean duration of prodrome in unipolar depression was significantly greater - Mann-Whitney U = 2.32; z = 3.22; $P = 0.001$ (significant even after Bonferroni correction). [d], Median duration of prodrome in unipolar depression was significantly greater - both according to the Mann Whitney test as above, and the Mood's Median test $X^2 = 8.51$; $P = 0.003$ (significant even after Bonferroni correction)

Table III. Common prodromal symptoms reported by both patients and their relatives

	Mania	N= 60[a] (%)	Unipolar depression	N = 60[b] (%)
1.	Hostility*	54 (90)	Sadness*	52 (90)
2.	Overactivity	52 (87)	Talking less*	46 (77)
3.	Ideas of grandiosity*	48 (80)	Lassitude*	46 (77)
4.	Meddling and arguing	46 (77)	Worrying over trifles*	46 (77)
5.	Reduced sleep	46 (77)	Autonomic disturbances*	44 (73)
6.	Does not need much sleep	44 (73)	Indecision*	42 (70)
7.	Irritability	44 (73)	Reduced appetite*	40 (67)
8.	Elation	42 (70)	Difficulty concentrating	40 (67)
9.	Pressure of speech	40 (67)	Slowness of movement*	40 (67)
10.	Overspending	36 (60)	Does not feel like seeing people*	40 (67)
11.	Distractibility*	34 (57)	Fatiguability	36 (60)
12.	Being uncooperative*	34 (57)	Inability to feel	34 (57)
13.	Senses seem sharper	32 (53)	Decreased sleep	34 (57)
14.	Increased self care	30 (50)	Irritability	30 (50)
15.	Less affectionate	28 (47)	Decreased self care	30 (50)
16.	Less responsible	28 (47)	Pessimistic thoughts	30 (50)
17.	Ideas of persecution*	24 (40)	Inner tension and agitation	26 (43)
18.	Concentration difficulty	24 (40)	Decreased sexual interest*	26 (43)
19.	Labile emotional experience	22 (37)	Diurnal variation of symptoms - worsening in morning	26 (43)
20.	Involved in many projects	22 (37)	Less responsible	22 (37)
21.	Increased sexual interest	20 (33)	Less affectionate	20 (33)

[a], 52 different symptoms were reported by both patients and relatives, when interviewed using the scale for prodromal symptoms. Only the 21 most common ones (reported by at least a third of the subjects in both groups) are shown here. Since there were no significant differences between patients and their relatives with regard to the number and type of prodromal symptoms reported, these results represent a combined account; [b], N = 60- consisting of 30 patients and their 30 relatives.

P values were also adjusted for multiple comparisons by using the Bonferroni correction; significance was set at 5% ($P = 0.05$); Bonferroni corrected *P* ($P = 0.05$/number of comparisons): 0.05/30 = 0.002; *These symptoms were significantly ($P<0.001$) more frequent among patients with mania and depression, respectively.

Among patients with mania, about half of the subjects (n=28) reported a number of additional symptoms during the unstructured evaluation. These 'idiosyncratic' prodromal symptoms included increased religiosity, taking decisions easily, reddening of eyes, being abusive, listening to loud music, recalling past events, and ideas of reference. However, no such 'idiosyncratic' symptoms were reported among patients with unipolar depression.

Discussion

Results of the current study regarding prodromal symptoms of mania had much in common with the somewhat scarce previous literature on the subject[7,11,12]. Accordingly, a high proportion of patients, 70 per cent in the current study, and 75-100 per cent in earlier ones, were able to identify prodromal symptoms. The average prodromal duration of about 3 wk in the present study was also similar to 2-4 wk period reported previously among patients with mania[7,11,12]. The most frequent prodromal symptoms of mania found in several prior reports[7,11,12] were sleep disturbances, overactivity, mood changes, increased self-worth, unusual thought content, and disinhibition. A similar profile was found in the current study, indicating that prodromal symptoms closely approximate the symptoms of the disorder itself. Thus, they can only be differentiated quantitatively, but not necessarily qualitatively, from the symptoms of the full-blown episodes[24,25]. About half the patients with mania reported 'idiosyncratic' symptoms unique to their prodromes. These constitute individual 'relapse signatures,' which are particularly valuable as early indicators of relapse[14,24,26]. The presence of both typical and 'idiosyncratic' symptoms indicates that prodromal symptoms result from a complex mixture of biology, psychological makeup and past experiences[7]. In this

study, a significantly higher number of patients with unipolar depression, than those with mania, were able to identify their prodromes. Similar high rates of detection have been occasionally reported in major depression[27]. Moreover, mean and median prodromal durations were significantly longer in unipolar depression, compared to mania. Other studies have also found that the build-up to mania is much more rapid than major depression[28]. These differences between mania and major depression suggest that the key mediating variable could be loss of insight, which appears to occur earlier in mania, leading to the lower detection and shorter prodromes[7].

However, the most noteworthy findings of this study concerned the ability of relatives to detect prodromes. In this regard, a significantly higher number of relatives, than patients with mania, were able to report prodromes. The length of prodrome as estimated by relatives was also slightly (though not significantly) longer than the patients' estimates; but, there were no significant differences in the type of symptoms reported by either relatives or patients. In contrast, no differences between relatives and patients were observed in unipolar depression. The only other study[26] that has carried out similar comparisons between patients with bipolar disorder and their relatives, found no differences either in the proportion of subjects who could detect prodromes, or in the type of symptoms reported.

Our study had some methodological problems including its retrospective design, which is prone to biased or distorted recall. However, assessments were carried out within 2 wk of remission, or earlier, so that the events preceding the relapse could be recalled with sufficient accuracy. The 6-month period prior to the episode, utilised to define prodromal symptoms, was necessitated by the long prodromes found in unipolar depression, and the wide variability in prodromal durations found in both mania and depression[11,28]. Since such a long period could lead to some overlap with premorbid traits and residual symptoms, every effort was made to distinguish these from prodromal symptoms. Though the eventual sample sizes were small, the study was adequately powered to detect differences between patients, and between patients and relatives, and only slightly under-powered (70% instead of the ideal 80%) to detect differences between relatives of both groups. Finally, though the instrument used to record prodromal symptoms was not a well-validated one, the recommended approach[28] of using items from validated symptom scales, augmented by an unstructured interview, was followed. Information from multiple sources was obtained to enhance the validity of findings.

Despite these limitations, the findings endorse the notion of a reasonably long prodrome of mania, which can be identified by a majority of the patients, and which is characterised by typical and 'idiosyncratic' symptoms. Additionally, comparisons with unipolar depression suggested that patients with mania appear to retain insight for a shorter period prior to relapse, leading to the lower detection and comparatively shorter prodromes. Hence, although the window of opportunity is shorter in mania, the need to intervene is probably greater. These prodromal characteristics of mania provide considerable support for the commonly employed technique of teaching patients to detect early symptoms of relapse to prevent acute episodes and their adverse consequences[14]. Finally, the fact that relatives appeared to be better at detecting prodromes than the patients with mania themselves, clearly indicates the need to involve family members in any intervention that utilises early detection of prodromal symptoms as a key strategy. Including relatives will not only make this process more efficient, but may also improve the chances of a successful outcome.

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