Prevalence and clinical correlates of residual symptoms in remitted patients with bipolar disorder: An exploratory study

Sandeep Grover, Subho Chakrabarti, Swapnajeet Sahoo
Department of Psychiatry, Postgraduate Institute of Medical Education and Research, Chandigarh, India

**ABSTRACT**

**Objective:** This cross-sectional study aimed to evaluate the prevalence and factors associated with residual symptoms (both depressive and manic) in subjects with bipolar disorder (BD).

**Materials and Methods:** A total of 844 subjects diagnosed BD with an illness of 2 years’ duration and minimum of two lifetime episodes and in clinical remission were evaluated for residual symptoms using Hamilton Depression Rating Scale (HAM-D) and Young Mania Rating Scale (YMRS). Based on the severity of residual symptoms, the study groups were divided into four groups.

**Results:** Sixty-nine percent of the subjects had residual depressive symptoms (i.e., HAM-D score in the range of 1–7) and 59% had residual manic symptoms (i.e., YMRS score in the range of 1–7). The most common residual depressive symptom was psychic anxiety (34%) followed by impaired insight (29%). The most common manic symptom was poor insight (31%) followed by sleep disturbances (25%). Subjects with both sets of residual symptoms had onset of BD at a relatively young age, when compared to those with only residual depressive symptoms. Presence of any comorbid physical illness and substance abuse disorder was significantly higher in those with both sets of residual symptoms.

**Conclusions:** The present study suggests that a substantial proportion of patients with BD have residual symptoms of both types. Comorbid physical illness and substance use were associated with residual symptoms. Identification and management of residual symptoms are highly essential to improve the overall outcome of patients with BD.

**Key words:** Bipolar disorder, depression, mania, residual symptoms

**INTRODUCTION**

Bipolar disorder (BD) is characterized by episodic and recurrent patterns of distinct mood episodes, which causes significant psychosocial disability.[1] Despite the availability of several treatment strategies, the longitudinal course of BD is characterized by low recovery rate, high recurrence rate, poor interepisodic functioning, and high prevalence of physical- and substance use-related comorbidities.[2,3]

Several studies have demonstrated that a significant proportion of patients with BD continue to have residual or subsyndromal symptoms during the interepisodic phase.[4,5] The significance of residual symptoms in BD is multidimensional and multifaceted. Residual or subsyndromal symptoms in BD have been shown to...
be strongly associated with social, occupational, and cognitive impairment.\cite{3,5} Residual depressive symptoms have an adverse impact on overall functioning, whereas residual manic symptoms have a negative impact on financial issues, family stigma, interpersonal relationships, sexual functioning, and occupational stigma.\cite{3} Further, studies evaluating the course of residual symptoms have demonstrated that the intensity of residual symptoms and functional impairment in remitted BD patients decreases as the duration of remission increases.\cite{5} Residual depressive symptoms have been linked with shorter time to depressive recurrence, while residual manic symptoms have been found to be linked with shorter time to manic, hypomanic, or mixed recurrences.\cite{9,10} Evidence also suggests a strong association of residual mood symptoms with poor sleep quality, which has been found to independently predict the recurrence of mood episode.\cite{11}

In addition, depressive residual symptoms in patients with BD have been found to be associated with lower adherence to medication.\cite{12} Findings from the Systematic Treatment Enhancement Program for BD (STEP-BD) study suggest that in patients with bipolar depression with concurrent manic symptoms, the use of adjunctive antidepressant does not hasten time to recovery and may actually lead to greater manic residual symptom severity.\cite{13}

Despite these well-established facts on the significance of residual symptoms, there are several problems with the existing research. First, there is currently no explicit definition of residual symptoms in BD.\cite{14} In the absence of a clear definition of residual symptoms, studies have used various cutoffs to define residual symptoms. The International Task Force for BDs suggests that a Young Mania Rating Scale (YMRS) score of <8 or <5 should be used to define residual manic symptoms.\cite{15} Some authors have employed a threshold of YMRS score <7, with no core item of the YMRS (i.e., irritability, speech, content, and disruptive-aggressive behaviors) and having a score >2 to define residual symptoms.\cite{16,17} Similarly, remission for bipolar depression has been proposed as either a Hamilton Depression Rating Scale score (HAM-D 17) of ≤7 or ≤5,\cite{1,18} Montgomery Asberg Depression Rating Scale score of ≤7 or ≤5,\cite{19} or Bipolar Depression Rating Scale of ≤8.\cite{5} Moreover, most of the available studies on residual symptoms have focused on only one set of residual symptoms, either the prevalence of residual manic symptoms\cite{3,5,20} or the prevalence of residual depressive symptoms.\cite{6,21-26} Only a limited number of studies have explored both residual depressive and manic symptoms in the same patient sample.\cite{27-29} In terms of impact of residual symptoms, available evidence suggests that residual depressive symptoms have negative impact on functional outcome.\cite{8,23-25,30,31} A qualitative study which evaluated the opinions of 46 French psychiatrists for psychiatrists' therapeutic objectives and patient's complaints in bipolar depressed patients revealed that eight major residual symptoms in BD include suicidal risk, emotional dysfunction, observance, cognitive impairment, sleep disorder, functional disability, patient's complaints, and comorbidities' evolution.\cite{14} However, only a few studies have evaluated the role of comorbid conditions (e.g., physical illness and substance use disorders) on the residual symptoms.\cite{32}

Accordingly, the present study aimed to explore the residual symptoms (both depressive and manic) in subjects with BD in remission. Additional aim of the study was to evaluate the factors associated with the presence of residual symptoms.

**MATERIALS AND METHODS**

This cross-sectional study was carried out at a multispecialty tertiary care teaching hospital, which provides services to a major part of North India. This study was approved by the institute’s ethics committee, and all the participants were recruited after obtaining written informed consent. To be included in the study, the participants were required to fulfill the diagnosis of BD as per the DSM-IV criteria and assessed using the Mini International Neuropsychiatric Interview-Extended Version (MINI-PLUS 6.0 version).\cite{24} Participants were required to be aged 18 years or more, having illness duration of at least 2 years, and minimum of two lifetime episodes (BD-I or BD-II). They had to be in remission for a minimum of 3 months before induction. Remission was defined cross-sectionally as scores of ≤7 on the HAM-D-17\cite{7} and ≤7 on the YMRS.\cite{26} In addition, participants had to be “clinically stable” for the past 3 months, defined as no change in medications or dosages of medications in the past 3 months. To increase the reliability of information about recent and past episodes, information obtained from the patient was cross-checked with relatives who were staying with them and involved in their care. Patients with medical or substance-induced BD, those with intellectual disability, and those not willing to participate in the study were excluded from the study.

**Assessments**

Apart from the MINI-PLUS, the HAM-D, and the YMRS, the principal instrument used was the Retrospective Life Chart Form of the NIMH-Patient version.\cite{37} The LCM-S/R is an easy to follow self-reported method of constructing a clear picture of the longitudinal course of BD. The life chart provides an overview of the number and type of past episodes and their duration, frequency, and response to treatment. Retrospective life chart ratings are recorded by month and year in the form of a graph, with episodes recorded at four well-defined levels of severity. Information was obtained from patient, relatives, and review of treatment records. Information was extracted from the LCM of each individual patient for age of onset, number of episodes in the life chart (mania, depression, hypomania, and mixed affective state), and severity of episodes. MINI-Plus was used to assess for any comorbid psychiatric...
conditions. The patients were evaluated clinically during assessment, and their treatment records were reviewed for the presence/absence of any comorbid physical illnesses.

**Statistical analysis**

Statistical analyses were performed using Statistical Package for the Social Sciences Version 14.0 software (SPSS for Windows, Chicago, SPSS Inc.). The obtained data were analyzed using descriptive statistics, such as frequency, percentage, mean, and standard deviation (SD). Parametric statistics such as ANOVA and Student’s *t*-test and nonparametric statistics such as Chi-square test and Mann–Whitney-U-test were used for comparison. Post hoc comparison test (Scheffe test) was used to analyze the multiple pairwise differences in ANOVA more accurately. Kruskal–Wallis test was used to compare the pairwise differences in case of nonparametric data.

Pearson’s or Spearman’s correlation coefficients were used to determine the association of residual symptoms with demographic and clinical variables.

**RESULTS**

A total of 844 patients with BD currently in remission according to the selection criteria formed the study sample. Of the 844 participants, 581 (69%) of the patients had HAM-D score in the range of 1–7 while 499 (59%) had residual manic symptoms as indicated by YMRS score of 1–7. Based on the presence or absence and severity of residual symptoms, the study sample was divided into four groups, i.e., Group I – subjects with no residual symptoms (i.e., scores in both HDRS and YMRS equal to zero; (*n* = 175; 21%), Group II – subjects with only depressive residual symptoms (i.e., score of 0 on the YMRS and a HAM-D score ranging from 1 to 7; *n* = 170; 20%), Group III – subjects with only manic residual symptoms (i.e., score of 0 on HAM-D and YMRS score ranging from 1 to 7; *n* = 88; 10%), and Group IV – subjects with both depressive and manic residual symptoms (i.e., both HAM-D and YMRS scores >1 and less than equal to 7; *n* = 411; 49%).

**Sociodemographic profile of the four groups**

The mean age of the study sample was 39.82 (SD: 12.04) years; the majority of the participants were males (68%), were married (80%), and were currently employed (62%). There were no significant differences among the four groups in terms of demographic variables except that there were more unemployed subjects in the Group III (those with only residual manic symptoms) and higher proportion of those in Group IV belonging to nuclear family and rural backgrounds (those with both types of residual symptoms) [Table 1].

**Prevalence of residual depressive and manic symptoms**

Of the total study sample of 844 patients, 821 patients had BD-1 while 23 patients had BD-II. The most common residual depressive symptoms in the entire sample according to the HAM-D were psychic anxiety (34%), followed by impairment in insight (acknowledges being ill but attributes illness to external causes, 29.0%), loss of interest in work/activities (28%), and early insomnia (22%). However, the most common depressive residual symptom among those who had only depressive residual symptoms (Group II) was lack of interest in work/activities (35%), followed by psychotic anxiety (32%) and depressed mood (29%). In those who had both residual depressive and manic residual symptoms, the most common residual depressive symptom was poor insight (57%), followed by psychic anxiety (560%) and lack of interest in work/activities (43%).

Similarly, when the prevalence of residual manic symptoms as per the YMRS in the entire sample was analyzed (with no core items of YMRS, i.e., irritability, speech, content, and disruptive-aggressive behavior having a score >2), it was seen that the most common residual manic symptom was poor insight (i.e., either admits behavior change or possible behavior change, but denies illness, 31%), followed by sleep disturbance (i.e., sleeping less than normal amount by up to 1 h, 25%) and language-thought disorder (i.e., circumstantial; mild distractibility, 13%) [Table 2].

Poor insight (i.e., either admits behavior change or possible behavior change, but denies illness, 62%) was the most common manic symptom in Group IV (those with both depressive and manic residual symptoms), which was followed by sleep disturbance (44%) and language-thought disorder (26%). However, in those with only residual manic symptoms (Group III), the most common residual manic symptom was sleep disturbances (39%), followed by irritability (38%), elevated mood (33.0%), and appearance (23%) [Table 2].

**Clinical profile of the four groups**

The mean age of onset for the study sample was 28.23 (SD: 10.47) years. Subjects with both sets of residual symptoms (Group IV) had onset of BD at a relatively young age, when compared to those with only residual depressive symptoms (Group II) [Table 3].

Any comorbid physical illness was present in about 18% of the subjects with significantly higher prevalence of comorbid physical illnesses in those with both sets of residual symptoms (Group-IV). In terms of diabetes mellitus, hypertension, and hypothyroidism, too, those with both sets of residual symptoms had significantly higher prevalence of these illnesses.

Other physical illnesses were not present in subjects in Group III (those with only residual manic symptoms), while more subjects in the Group I (those with no residual symptoms of either polarity) had other physical illness (other than hypertension, diabetes mellitus, and hypothyroidism).
### Table 1: Sociodemographic profile of the study sample

| Sociodemographic variables | Whole sample (n=844) | Group I: No residual symptoms (HDRS and YMRS=0) (n=175) | Group II: Only depressive residual symptoms (YMRS=0 and HDRS=1-7) (n=170) | Group III: Only manic symptoms (YMRS=0 and HDRS >1-7) (n=88) | Group IV: Both depressive and manic symptoms (both HDRS and YMRS >1-7) (n=411) | Chi-square value/ANOVA with post hoc Scheffé’s test (P) |
|---------------------------|---------------------|----------------------------------------------------------|------------------------------------------------------------------------|-------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Age (years)               | 39.82 (12.04); 16-69 | 39.97 (12.21); 16-63                                      | 41.95 (11.88); 18-65                                                  | 38.17 (11.35); 18-65                                                   | 39.22 (12.10); 16-69                                                    | $F=2.692 (0.045)^* $df=3; II=I=IV=III |
| Gender                    | Male                | 570 (67.5)                                               | 111 (63.4)                                                            | 107 (62.9)                                                             | 57 (64.8)                                                                  | 295 (71.8)                                                                  | 6.660 (0.084) |
|                           | Female              | 274 (32.5)                                               | 64 (36.6)                                                             | 63 (37.1)                                                              | 31 (35.2)                                                                  | 116 (28.2)                                                                  | |
| Current marital status    | Currently single    | 169 (20.0)                                               | 44 (25.1)                                                             | 24 (14.1)                                                              | 16 (18.2)                                                                  | 85 (20.7)                                                                  | 6.864 (0.076) |
|                           | Currently married   | 675 (80.0)                                               | 131 (74.9)                                                            | 146 (85.9)                                                            | 72 (81.8)                                                                  | 326 (79.3)                                                                  | |
| Education - number of years | 11.37 (3.87); 0-20 | 11.25 (3.93); 0-20                                       | 11.51 (4.28); 0-20                                                   | 11.29 (4.22); 0-18                                                    | 11.39 (3.60); 0-18                                                       | $F=2.284 (0.944) $II-IV=III=I |
| Current employment status | Currently unemployed| 321 (38.0)                                               | 56 (32.0)                                                             | 59 (34.7)                                                              | 12 (13.6)                                                                  | 194 (47.2)                                                                  | 40.386 |
|                           | Currently employed  | 523 (62.0)                                               | 119 (68.0)                                                            | 111 (65.3)                                                            | 76 (86.4)                                                                  | 217 (52.8)                                                                  | $<0.001^{***}$ |
| Family type               | Nuclear             | 482 (57.1)                                               | 75 (42.9)                                                             | 83 (48.8)                                                              | 39 (44.3)                                                                  | 285 (69.3)                                                                  | 50.267 |
|                           | Non-nuclear         | 362 (42.9)                                               | 100 (57.1)                                                            | 87 (51.2)                                                              | 49 (55.7)                                                                  | 126 (30.7)                                                                  | $<0.001^{***}$ |
| Locality                  | Urban               | 403 (47.7)                                               | 88 (50.3)                                                             | 96 (56.5)                                                              | 44 (50.0)                                                                  | 175 (42.6)                                                                  | 10.216 (0.017)^* |
|                           | Rural               | 441 (52.3)                                               | 87 (49.7)                                                             | 74 (43.5)                                                              | 44 (50.0)                                                                  | 236 (57.4)                                                                  | |

SD = Standard deviation; YMRS = Young Mania Rating Scale; HDRS = Hamilton Depression Rating Scale

### Table 2: Prevalence of residual depressive and manic symptoms

| Item number | HDRS scale - residual depressive symptoms | Frequency in the entire sample (n=844), n (%) | Frequency in the Group II (those with only depressive residual symptoms) (n=170), n (%) | Frequency in the Group IV (those with both depressive and manic residual symptoms) (n=411), n (%) |
|-------------|------------------------------------------|---------------------------------------------|-----------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|
| 1           | Depression                               | 99 (11.7)                                   | 50 (29.4)                                                                                     | 49 (11.9)                                                                                           |
| 2           | Feelings of guilt                        | 36 (4.3)                                    | 12 (7.1)                                                                                      | 24 (5.8)                                                                                            |
| 3           | Suicide                                  | 48 (5.7)                                    | 12 (7.1)                                                                                      | 36 (8.8)                                                                                            |
| 4           | Insomnia - early                         | 183 (21.7)                                  | 27 (15.9)                                                                                     | 156 (38.0)                                                                                         |
| 5           | Insomnia - middle                        | 58 (6.9)                                    | 19 (11.2)                                                                                     | 39 (9.5)                                                                                            |
| 6           | Insomnia - late                          | 64 (7.6)                                    | 23 (13.5)                                                                                     | 41 (10.0)                                                                                          |
| 7           | Work/activities                          | 238 (28.2)                                  | 60 (35.3)                                                                                     | 178 (43.3)                                                                                         |
| 8           | Retardation                              | 33 (3.9)                                    | 25 (14.7)                                                                                     | 8 (1.9)                                                                                             |
| 9           | Agitation                                | 101 (12.0)                                  | 28 (16.5)                                                                                     | 73 (17.8)                                                                                          |
| 10          | Anxiety-psychoic                         | 286 (33.9)                                  | 56 (32.9)                                                                                     | 230 (56.0)                                                                                         |
| 11          | Anxiety-somatic                          | 150 (17.8)                                  | 37 (21.8)                                                                                     | 113 (27.5)                                                                                         |
| 12          | Somatic symptoms - gastrointestinal      | 147 (17.4)                                  | 31 (18.2)                                                                                     | 116 (28.2)                                                                                         |
| 13          | Somatic symptoms - general               | 71 (8.4)                                    | 35 (20.6)                                                                                     | 36 (8.8)                                                                                            |
| 14          | Genital symptoms                         | 28 (3.3)                                    | 18 (10.6)                                                                                     | 10 (2.4)                                                                                            |
| 15          | Hypochondriasis                          | 14 (1.7)                                    | 11 (6.5)                                                                                      | 3 (0.7)                                                                                             |
| 16          | Weight loss                              | 41 (4.9)                                    | 7 (4.1)                                                                                       | 34 (8.3)                                                                                            |
| 17          | Insight                                  | 245 (29.0)                                  | 9 (5.3)                                                                                       | 235 (57.2)                                                                                         |

| Item number | YMRS - residual manic symptoms           | Frequency in the entire sample (n=844), n (%) | Frequency in the Group III (those with only residual manic symptoms) (n=88), n (%) | Frequency in the Group IV (those with both depressive and manic residual symptoms) (n=411), n (%) |
|-------------|------------------------------------------|---------------------------------------------|-----------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|
| 1           | Elevated mood                            | 66 (7.8)                                    | 29 (33.0)                                                                                     | 37 (9.0)                                                                                           |
| 2           | Increased motor activity/energy          | 89 (10.5)                                   | 10 (11.4)                                                                                     | 79 (19.2)                                                                                          |
| 3           | Sexual interest                          | 20 (2.4)                                    | 8 (9.1)                                                                                       | 12 (2.9)                                                                                            |
| 4           | Sleep                                    | 213 (25.2)                                  | 34 (38.6)                                                                                     | 179 (43.6)                                                                                         |
| 5           | Irritability                             | 83 (9.8)                                    | 33 (37.5)                                                                                     | 50 (12.2)                                                                                          |
| 6           | Speech (rate/amount)                     | 43 (5.1)                                    | 6 (6.8)                                                                                       | 37 (9.0)                                                                                            |
| 7           | Language-thought disorder                | 109 (12.9)                                  | 4 (4.5)                                                                                       | 105 (25.5)                                                                                         |
| 8           | Content                                  | 8 (0.9)                                     | 0 (0)                                                                                         | 8 (1.9)                                                                                             |
| 9           | Disruptive/aggressive behavior           | 9 (1.1)                                     | 4 (4.5)                                                                                       | 5 (1.2)                                                                                             |
| 10          | Appearance                               | 71 (8.4)                                    | 20 (22.7)                                                                                     | 51 (12.4)                                                                                          |
| 11          | Insight                                  | 263 (31.2)                                  | 7 (8.0)                                                                                       | 256 (62.3)                                                                                         |

YMRS = Young Mania Rating Scale; HDRS = Hamilton Depression Rating Scale
Table 3: Clinical profile of the study sample

| Clinical variables                                | Whole sample (n=844) | Group I No residual symptoms (HDRS and YMRS=0) (n=175) | Group II Only depressive residual symptoms (YMRS=0 and HDRS=1-7) (n=170) | Group III Only manic symptoms (HDRS=0 and YMRS >1-7) (n=88) | Group IV Both depressive and manic symptoms (both HDRS and YMRS >1-7) (n=411) | Chi-square value/ANOVA F value with post hoc Scheffe’s test/Kruskal-Wallis value (P) |
|--------------------------------------------------|----------------------|------------------------------------------------------|------------------------------------------------------------------------|-----------------------------------------------------------------|---------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Age of onset (years)                              | 28.23 (10.47); 13-61| 28.71 (11.61); 13-57                                  | 29.97 (11.12); 13-60                                                 | 29.31 (10.26); 13-54                                            | 27.07 (9.81); 13-61                                                              | F=3.725 (0.011)* II-IV***; II-I-III-IV                                        |
| Comorbid physical illness                         |                      |                                                      |                                                                        |                                                                 |                                                                                |                                                                                  |
| Any comorbid physical illness: Present            | 151 (17.9)           | 19 (10.9)                                            | 25 (14.7)                                                             | 4 (4.5)                                                         | 103 (25.1)                                                                      | 32.120 (<0.001)***                                                                 |
| Hypertension only                                | 47 (5.6)             | 2 (1.1)                                              | 6 (3.5)                                                               | 2 (2.3)                                                         | 37 (9.0)                                                                        | 18.896 (<0.001)***                                                          |
| Diabetes mellitus only                           | 27 (3.2)             | 1 (0.6)                                              | 3 (0.6)                                                               | 0                                                               | 23 (5.6)                                                                        | 15.565 (0.001)***                                                           |
| HTN and DM both                                  | 14 (1.7)             | 1 (0.6)                                              | 5 (2.9)                                                               | 0 (0)                                                           | 8 (1.9)                                                                         | 4.675 (0.197)                                                               |
| Hypothyroidism: Present                          | 50 (5.9)             | 5 (2.9)                                              | 5 (2.9)                                                               | 2 (2.3)                                                         | 38 (9.2)                                                                        | 15.909 (0.001)***                                                          |
| Comorbid substance use Subst. use disorder: Present| 139 (16.5)           | 14 (8.0)                                             | 22 (12.9)                                                             | 7 (8.0)                                                         | 96 (23.4)                                                                        | 29.477 (<0.001)***                                                               |
| Alcohol dependence                               | 82 (9.7)             | 11 (6.3)                                             | 19 (11.2)                                                             | 6 (6.8)                                                         | 46 (11.2)                                                                        | 4.624 (0.201)                                                                |
| Cannabis dependence                              | 11 (1.3)             | 0                                                     | 0                                                                    | 0                                                               | 11 (2.7)                                                                        | 11.742 (0.002)**                                                             |
| Tobacco dependence                               | 46 (5.5)             | 3 (1.7)                                              | 3 (1.8)                                                               | 1 (1.1)                                                         | 39 (9.5)                                                                        | 25.409 (<0.001)***                                                           |
| None                                             | 705 (83.5)           | 161 (92.0)                                           | 148 (87.1)                                                            | 81 (92.0)                                                       | 315 (76.6)                                                                      | 29.477 (<0.001)***                                                               |
| Life history of BPAD                              |                      |                                                      |                                                                        |                                                                 |                                                                                |                                                                                  |
| Mean number of manic episodes in the lifetime     | 3.38 (3.66); 0-31    | 4.12 (3.77); 1-21                                    | 3.48 (4.35); 0-28                                                    | 4.15 (4.46); 1-30                                               | 2.86 (2.98); 0-31                                                               | Kruskal-Wallis value-34.23 (<0.001)*** III-IV*; II-IV**                      |
| Mean number of depressive episodes in the lifetime| 2.89 (3.61); 0-30    | 2.43 (2.92); 0-21                                    | 3.55 (4.46); 0-30                                                    | 2.59 (2.92); 0-17                                               | 2.87 (3.59); 0-23                                                               | Kruskal-Wallis value-9.849 (0.020)** II-IV; IV-III-I; II-I*                   |
| Mean number of hypomanic episodes in the lifetime | 0.49 (2.09); 0-21    | 0.14 (0.51); 0-3                                     | 0.429 (1.82); 0-20                                                   | 0.15 (0.93); 0-8                                                | 0.739 (2.68); 0-21                                                               | Kruskal-Wallis value-16.994 (0.001)*** IV-I*; IV-II-III-I                  |
| Mean number of mixed episodes in the lifetime     | 0.065 (0.59); 0-16   | 0.005 (0.075); 0-1                                   | 0.052 (0.249); 0-2                                                   | 0.022 (0.213); 0-2                                              | 0.104 (0.83); 0-16                                                               | Kruskal-Wallis value-10.950 (0.012)** IV-III-IV                             |
| Mean number of total episodes in the lifetime     | 6.83 (6.56); 1-55    | 6.71 (5.52); 1-42                                    | 7.511 (7.98); 1-55                                                   | 6.920 (6.49); 2-40                                              | 6.58 (6.33); 1-53                                                               | Kruskal-Wallis value-7.876 (0.049)* II-III-IV                                   |
| Mean HDRS score                                   | 2.39 (2.02); 0-7     | 2.88 (1.34); 1-7                                     | 0                                                                    | 3.72 (1.45); 1-7                                               |                                                                                | Kruskal-Wallis value-586.61 (<0.001)*** IV-I-III-III-III***                    |
| Mean YMRS score                                   | 1.46 (1.58); 0-7     | 0                                                    | 2.36 (1.17); 1-5                                                     | 2.50 (1.34); 1-7                                               |                                                                                | Kruskal-Wallis value-666.33 (<0.001)*** FIV-III; IV-I-III***                   |
| Mean number of manic episodes per year of illness | 0.42 (0.55); 0-8     | 0.56 (0.67); 0.04-5.22                               | 0.39 (0.50); 0-4                                                     | 0.62 (0.91); 0.04-8                                            | 0.34 (0.36); 0-2.44                                                              | Kruskal-Wallis value-46.28 (<0.001)*** I-IV***; III-IV*** III-I-IV-IV         |
| Mean number of depressive episodes per year of illness| 0.33 (0.44); 0-5.22 | 0.36 (0.64); 0-5.22                                  | 0.34 (0.33); 0-2.05                                                  | 0.37 (0.40); 0-2                                               | 0.29 (0.39); 0-4                                                               | Kruskal-Wallis value-9.338 (0.025)** III-I-IV                                   |
| Mean number of hypomanic episodes per year of illness| 0.04 (0.20); 0-4    | 0.026 (0.14); 0-1.5                                  | 0.06 (0.34); 0-4                                                     | 0.029 (0.188); 0-1.6                                          | 0.048 (0.15); 0-1.21                                                          | Kruskal-Wallis value-16.439 (0.001)*** IV-II-III-IV                           |
| Mean number of mixed episodes per year of illness | 0.006 (0.045); 0-1   | 0.0003 (0.0037); 0-0.05                              | 0.006 (0.04); 0-0.4                                                  | 0.001 (0.019); 0.017                                         | 0.009 (0.059); 0-1                                                              | Kruskal-Wallis value-11.063 (0.011)** IV-II-III-IV                           |
| Contd...                                          |                      |                                                      |                                                                        |                                                                 |                                                                                |                                                                                  |
Comorbid substance use disorder was present in about one-sixth (16.5%) of the subjects, with significantly higher prevalence among those with both sets of residual symptoms. The mean HDRS score of the study sample was 2.39 (±2.02) and the mean YMRS score was 1.46 (±1.58), with significantly higher HDRS and higher YMRS score for those with both sets of residual symptoms [Table 3].

Like the higher prevalence of physical comorbidity, the prevalence of substance abuse disorders were also significantly higher among those with both sets of residual symptoms (Group IV), especially cannabis and tobacco dependence [Table 3].

In terms of lifetime history of number of episodes, the mean number of manic episodes, depressive episodes, hypomanic episodes, and mixed episodes per year of illness was 0.44 (SD: 0.56), 0.33 (SD: 0.47), 0.05 (SD: 0.29), and 0.006 (SD: 0.048) episodes, respectively. Significantly higher numbers of manic episodes per year of illness were noted in the group with only residual manic symptoms, compared to the other two groups with residual symptoms and those with no residual symptoms. No significant group differences were found with respect to the mean number of depressive episodes, hypomanic episodes, and mixed episodes per year of illness. The mean number of total episodes per year of illness was 0.83 (SD: 0.96) for the whole study sample, with significantly higher number of mean total episodes seen in those only residual manic symptoms, compared to those with both sets of residual symptoms [Table 3].

**Treatment profile of four groups**

When the current treatment profile of the participants was evaluated, it was seen that about two-fifths of the sample (40.5%) were receiving a combination of a mood stabilizer and an antipsychotic, which was closely followed by the use of mood stabilizers only (37%) and use of combination of mood stabilizers and an antidepressant (11.5%) [Table 4].

When the four study groups were compared, it was seen that compared to other three groups, those with only residual depressive symptoms were less often receiving a combination of a mood stabilizer and an antipsychotic and more often receiving a combination of a mood stabilizer and an antidepressant. Compared to other three groups, those with both residual depressive and manic symptoms were more often receiving a combination of a mood stabilizer, an antipsychotic, and an antidepressant. Compared to other groups, those with no residual symptoms or residual manic symptoms were more often receiving only mood stabilizer.

With regard to specific antipsychotics, compared to other three groups, significantly higher proportions of participants with both residual depressive and manic symptoms were on olanzapine (41%) and higher numbers of participants with only residual manic symptoms were on clozapine (3%) as compared to other groups.

With regard to antidepressants, only one-fifth of the study sample was on antidepressants. In addition to receiving mood stabilizers, significantly higher number of subjects with only residual depressive symptoms was on escitalopram (7%), venlafaxine (5%), and bupropion (7%), compared to the other three groups. With regard to mood stabilizers, significantly less number of subjects with only manic residual symptoms were on lithium (51%), but significantly higher proportion of the subjects were on combination of two mood stabilizers (lithium and valproate), when compared to the other three groups [Table 4].

**Association of residual depressive symptoms in bipolar disorder with sociodemographic and clinical variables**

When the association of residual symptoms with demographic profile was evaluated in the whole sample, significantly higher depressive residual symptoms were present in males, among those who were unemployed, had comorbid physical illness, and had comorbid substance use disorder [Table 5]. Higher residual symptoms were associated with significantly lower mean number of manic episodes and mean number of total episodes of illness per year and significantly higher mean number of hypomanic episodes and mixed episodes per year of illness.
Table 4: Comparison of the treatment profile of 4 groups

| Clinical variables | Whole sample (n=844) | Group I (n=175) | Group II (n=170) | Group III (n=88) | Group IV (n=411) | Chi-square value (P) |
|--------------------|----------------------|-----------------|------------------|------------------|------------------|---------------------|
| Antipsychotics     |                      |                 |                  |                  |                  |                     |
| None               | 507 (48.2)           | 55 (54.3)       | 50 (51.1)        | 507 (48.2)       | 45 (52.3)        | 169 (41.1)          | 17.7 (0.007)***     |
| Olanzapine         | 273 (32.3)           | 33 (35.7)       | 29 (31.8)        | 273 (32.3)       | 20 (45.5)        | 127 (30.9)          | 16.669 (0.001)***   |
| Quetiapine         | 57 (6.8)             | 14 (14.0)       | 11 (11.8)        | 57 (6.8)         | 21 (5.1)         | 21 (5.1)            | 4.09 (0.251)        |
| Aripiprazole       | 14.1 (7.7)           | 4.2 (4.2)       | 2.5 (2.5)        | 14 (1.7)         | 1.7 (1.7)        | 1.824 (0.669)       |                     |
| Ziprasidone        | 1.0 (0.1)            | 0.0 (0.0)       | 0.0 (0.0)        | 1.0 (0.1)        | 0.0 (0.0)        | 1.0 (0.0)           |                     |
| Clozapine          | 7.0 (0.8)            | 1.0 (1.0)       | 1.0 (1.0)        | 7.0 (0.8)        | 1.0 (1.0)        | 1.0 (1.0)           | 9.272 (0.026)*      |
| Lurasidone         | 1.0 (0.1)            | 0.0 (0.0)       | 0.0 (0.0)        | 1.0 (0.1)        | 0.0 (0.0)        | 1.0 (1.0)           |                     |
| Trifluoperazine    | 13.1 (5.1)           | 1.0 (1.0)       | 1.0 (1.0)        | 13.1 (5.1)       | 1.0 (1.0)        | 1.0 (1.0)           | 1.99 (0.574)        |
| Chlorpromazine     | 3.0 (0.4)            | 1.0 (1.0)       | 1.0 (1.0)        | 3.0 (0.4)        | 1.0 (1.0)        | 1.0 (1.0)           |                     |
| Antidepressants    |                      |                 |                  |                  |                  |                     |                     |
| None               | 674 (79.9)           | 157 (89.7)      | 118 (69.4)       | 674 (79.9)       | 80 (90.9)        | 319(77.6)           | 30.068 (<0.001)***  |
| Escitalopram       | 34 (4.0)             | 2.1 (1.1)       | 1.0 (1.0)        | 34 (4.0)         | 1.0 (1.0)        | 1.0 (1.0)           | 10.086 (0.017)*     |
| Paroxetine         | 18 (2.1)             | 5.0 (2.9)       | 2.0 (2.0)        | 18 (2.1)         | 2.0 (2.0)        | 7 (1.7)             | 1.754 (0.624)       |
| Fluoxetine         | 22 (2.6)             | 2.1 (1.1)       | 1.0 (1.0)        | 22 (2.6)         | 1.0 (1.0)        | 1.0 (1.0)           | 3.210 (0.360)       |
| Paroxetine         | 11 (1.3)             | 0.0 (0.0)       | 0.0 (0.0)        | 11 (1.3)         | 0.0 (0.0)        | 11 (1.3)            |                     |
| Venlafaxine        | 23 (2.7)             | 1.0 (1.0)       | 0.0 (0.0)        | 23 (2.7)         | 0.0 (0.0)        | 12 (2.9)            | 8.191 (0.042)*      |
| Mirtazapine        | 26 (3.1)             | 0.0 (0.0)       | 0.0 (0.0)        | 26 (3.1)         | 0.0 (0.0)        | 17 (4.1)            |                     |
| Bupropion          | 29 (3.4)             | 6.0 (6.0)       | 4.0 (4.0)        | 29 (3.4)         | 4.0 (4.0)        | 10 (2.4)            | 9.373 (0.024)*      |
| Amitriptyline      | 7.0 (0.8)            | 2.1 (1.1)       | 2.0 (2.0)        | 7.0 (0.8)        | 2.0 (2.0)        | 2 (0.5)             | 1.146 (0.765)       |
| Mood stabilizers   |                      |                 |                  |                  |                  |                     |                     |
| None               | 32 (3.8)             | 5.0 (2.9)       | 13 (7.6)         | 32 (3.8)         | 3.0 (1.0)        | 11 (2.7)            | 8.783 (0.032)*      |
| Lithium            | 518 (61.4)           | 114 (65.1)      | 91 (53.5)        | 518 (61.4)       | 5 (0.8)          | 268 (65.2)          | 11.899 (0.007)**    |
| Valproate          | 241 (28.6)           | 46 (26.3)       | 57 (33.5)        | 241 (28.6)       | 46 (26.3)        | 114 (27.2)          | 2.709 (0.438)       |
| Carbamazepine      | 9.1 (1.1)            | 1.0 (1.0)       | 2.0 (2.0)        | 9.1 (1.1)        | 1.0 (1.0)        | 4 (1.0)             | 1.673 (0.642)       |
| Valproate + lithium| 38 (4.6)             | 9.5 (5.1)       | 6.0 (3.5)        | 38 (4.6)         | 9.5 (5.1)        | 14 (2.5)            | 30.473 (<0.001)***  |
| Lamotrigine        | 5.0 (0.6)            | 0.0 (0.0)       | 0.0 (0.0)        | 5.0 (0.6)        | 1.0 (0.0)        | 4 (1.0)             |                     |

*P<0.05; **P<0.01; ***P<0.001. MS – Mood stabilizers; AP – Antipsychotics; AD – Antidepressants; YMRS – Young Mania Rating Scale; HDRS – Hamilton Depression Rating Scale; SD – Standard deviation

Table 5: Association of residual symptoms with clinical variables (continuous)

| Clinical variables | Total HDRS score r (P) | Total YMRS score r (P) |
|--------------------|------------------------|------------------------|
| Age (years)        | -0.022 (0.521)         | -0.117 (0.001)***      |
| Age of onset (years) | -0.082 (0.017)*        | -0.112 (0.001)***      |
| Mean number of manic episodes per year of illness | -0.178 (<0.001)*** | -0.018 (0.594)* |
| Mean number of depressive episodes per year of illness | 0.007 (0.834)* | -0.030 (0.382)* |
| Mean number of hypomanic episodes per year of illness | 0.102 (0.003)** | 0.054 (0.119)* |
| Mean number of mixed episodes per year of illness | 0.093 (0.007)** | 0.076 (0.027)** |
| Mean number of total episodes per year of illness | -0.076 (0.027)** | -0.010 (0.781)* |

*Spearmean co-efficient; **P<0.05; ***P<0.01; ****P<0.001. YMRS – Young Mania Rating Scale; HDRS – Hamilton Depression Rating Scale

Episodes and mixed episodes of illness per year. Those who were receiving mood stabilizer and antidepressants combination, those receiving combination of mood stabilizer, antipsychotics, and antidepressants, and those on mood stabilizer alone had significantly lower residual depressive symptoms [Tables 5 and 6].

Association of residual manic symptoms/Young Mania Rating Scale scores in bipolar disorder with sociodemographic and clinical variables

Compared to females, males had significantly higher mean residual manic symptoms. Further, the mean residual manic symptoms were significantly higher...
among those who were unemployed and belonged to rural background. Presence of comorbid physical illnesses and comorbid substance use disorder also was associated with significantly higher residual manic symptoms. Younger age at presentation and younger age of onset were associated with significantly higher residual manic symptoms. Residual manic symptoms were found to have significant association with only mean number of mixed episodes per year of illness but not with any other parameters of BD.

Those on a combination of mood stabilizer and antipsychotics, on a combination of mood stabilizer, antipsychotics, and antidepressants, and on mood stabilizer alone had significantly higher mean residual manic symptoms [Tables 5 and 7],

Table 6: Association of residual Hamilton Depression Rating Scale scores with clinical variables (noncontinuous)

| Variables                  | Mean HDRS score | t-value/Mann-Whitney value (P) |
|----------------------------|-----------------|--------------------------------|
| Gender                     |                 |                                |
| Male                       | 2.52 (2.04)     | $t$=2.714 (0.007)**            |
| Female                     | 2.12 (1.95)     |                                |
| Marital status             |                 |                                |
| Single                     | 2.25 (1.96)     | $t$=−1.015 (0.310)             |
| Married                    | 2.43 (2.03)     |                                |
| Occupation                 |                 |                                |
| Unemployed                 | 2.80 (1.94)     | $t$=4.645 (<0.001)***          |
| Employed                   | 2.14 (2.02)     |                                |
| Locality                   |                 |                                |
| Urban                      | 2.30 (2.04)     | $t$=−1.277 (0.202)             |
| Rural                      | 2.48 (2.00)     |                                |
| Any comorbid physical illness |              |                                |
| Present                    | 3.15 (1.87)     | $t$=5.193 (<0.001)***          |
| Absent                     | 2.22 (2.01)     |                                |
| Substance use disorder     |                 |                                |
| Present                    | 3.23 (1.87)     | $t$=5.408 (<0.001)***          |
| Absent                     | 2.23 (2.01)     |                                |
| Treatment profile          |                 |                                |
| MS + AP                    | 2.44 (2.08)     | $t$=0.577 (0.564)              |
| Absent                     | 2.36 (1.98)     |                                |
| MS + AD                    | 1.51 (1.60)     | U=31188.0 (0.023)*             |
| Absent                     | 2.34 (2.03)     |                                |
| MS + AD + AP               | 3.15 (1.69)     | $t$=3.127 (0.002)**            |
| Absent                     | 2.33 (2.03)     |                                |
| MS only                    | 2.02 (1.99)     | $t$=−4.120 (<0.001)***         |
| Absent                     | 2.61 (2.00)     | <0.001                        |
| AP only                    | 2.27 (2.09)     | $t$=−2.289 (0.773)             |
| Absent                     | 2.39 (2.02)     |                                |
| AP + AD                    | 3.60 (1.42)     | $t$=1.896 (0.058)              |
| Absent                     | 2.38 (2.02)     |                                |

$^*P<0.05; ~**P<0.01; ~***P<0.001$. MS – Mood stabilizers; AP – Antipsychotics; AD – Antidepressants; HDRS – Hamilton Depression Rating Scale

DISCUSSION

Prevalence of residual symptoms

The present study shows that about 69% of the patients with BD have residual depressive symptoms and 59% of the participants had residual manic symptoms. The study also revealed that almost half of the participants (48.7%) have both depressive and manic residual symptoms. Although there is lack of consensus on the definition of residual symptoms, the reported prevalence in the existing literature is in the range of 14%–70%. Findings of the present study also support the same.

Symptomatology of residual symptoms in bipolar disorder

Studies have explored the residual depressive symptoms in patients with BD and have reported cognitive symptoms to be more common. Data from STEP-BD trial which evaluated residual symptoms on MADRS reported sadness, lassitude, inability to feel, and pessimistic thoughts, whereas other studies have reported depressed mood, somatic anxiety, impact on work and activities, psychic anxiety, and gastrointestinal and somatic symptoms to be the common residual symptoms. In the present study, the most common residual depressive symptom in the entire sample as per the HDRS was psychic anxiety (33.9%) followed by poor insight (acknowledges being ill but attributing to external causes, 29.0%), loss of interest in work/activities, and early insomnia. In addition, the type and frequency of depressive residual symptoms slightly varied in the subgroups (Group II and Group IV). When the findings of the present study are compared with the available literature, it is apparent that psychic anxiety, impact on functioning/loss of interest in work, and sleep disturbances are the most common residual depressive symptoms in patients with BD. Accordingly, it can be said that efforts must be made to address the anxiety and sleep problems among patients with BD even during the interepisodic phase.

Findings of the present study suggest that the most common manic residual symptoms were poor insight followed by sleep disturbances and language-thought disorder to be the most common residual manic symptoms. Further, the nature and types of manic residual symptoms were different among the two subgroups of subjects with residual manic symptoms (Group III and Group IV). Sleep disturbances were one of the most common manic residual symptoms in the present study, which is in line with the previous literature. Other studies which have YMRS also suggest that besides decrease in sleep, other common residual manic symptoms include increase in verbal activity, motor activity, and hostility as the most common residual symptoms in patients with BD. Available evidence also suggests that sleep disturbance is one of the strongest predictors of manic relapse. Accordingly, it can be said that clinicians managing patients with BD should address sleep disturbances adequately.
Table 7: Association of residual Young Mania Rating Scale scores with clinical variables (noncontinuous)

| Variables                  | Mean YMRS score | t (P)   |
|----------------------------|----------------|---------|
| Gender                     |                |         |
| Male                       | 1.56 (1.61)    | t=2.508 (0.012)* |
| Female                     | 1.27 (1.51)    |         |
| Marital status             |                |         |
| Single                     | 1.63 (1.73)    | t=1.581 (0.114) |
| Married                    | 1.42 (1.54)    |         |
| Occupation                 |                |         |
| Unemployed                 | 1.70 (1.69)    | t=3.428 (0.001)*** |
| Employed                   | 1.32 (1.49)    |         |
| Religion                   |                |         |
| Hindu                      | 1.34 (1.53)    | t=−3.481 |
| Non-Hindu                  | 1.76 (1.66)    | (0.001)*** |
| Locality                   |                |         |
| Urban                      | 1.34 (1.57)    | t=−2.140 (0.033)* |
| Rural                      | 1.57 (1.58)    |         |
| Any comorbid physical illness |            |         |
| Present                    | 1.83 (1.57)    | U=43105.0 |
| Absent                     | 1.38 (1.57)    | (<0.001)*** |
| Substance use disorder     |                |         |
| Present                    | 1.90 (1.61)    | t=3.603 |
| Absent                     | 1.38 (1.56)    | (<0.001)*** |
| Treatment profile          |                |         |
| MS + AP                    |                |         |
| Present                    | 1.68 (1.65)    | U=74658.0 |
| Absent                     | 1.31 (1.52)    | (0.001)*** |
| MS + AD                    |                |         |
| Present                    | 1.11 (1.36)    | U=31327.0 |
| Absent                     | 1.51 (1.60)    | (0.023)* |
| MS + AD + AP               |                |         |
| Present                    | 1.79 (1.57)    | U=20987.0 |
| Absent                     | 1.44 (1.58)    | (0.043)* |
| AP only                    |                |         |
| Present                    | 1.31 (1.54)    | U=75138.0 |
| Absent                     | 1.55 (1.60)    | (0.020)* |
| AP + AD                    |                |         |
| Present                    | 0.86 (1.35)    | U=6945.0 (0.052) |
| Absent                     | 1.48 (1.58)    |         |

**Association of residual symptoms with sociodemographic parameters**

In the present study, very few demographic factors were found to have any significant association with residual symptoms. Residual symptoms were common among those who were unemployed and were from rural locality. Similar findings have been reported by a previous study from India. However, studies from the Western countries have not found similar association. Accordingly, it can be said that possibly, cultural and psychosocial factors, specific to India, may play a role in manifestation of these residual symptoms and future studies must attempt to look in depth into these associations.

There is limited literature on association of residual symptoms with gender. Studies which have evaluated the association of residual symptoms with gender suggest that males have higher subsyndromal manic symptoms, whereas females have been reported to have higher subsyndromal depressive symptoms. However, in the present study, both residual depressive and manic symptoms were found to be higher in males. This could be possibly because of higher representation of males in the study sample, which is usual in Indian studies on BD, i.e., greater males proportion in the study population.

**Association of residual symptoms with clinical parameters**

Present study suggests that patients with younger age of onset of illness have higher prevalence and higher severity of residual symptoms. Previous studies, which have evaluated the relationship of age of onset of BD and functional outcome, suggest that younger age of onset is associated with poorer outcome with more lifetime episodes, more frequent recurrences, more comorbidities, and increased time to recovery. Although the present study was not designed to evaluate these outcomes, yet it can be postulated that younger age of onset possibly linked with greater residual symptoms could be a reason for poor outcome in BD.

Participants with BD have been found to have a high degree of comorbid substance abuse and comorbid psychiatric disorders. However, whether these comorbidities have any impact on residual symptoms is still unknown. Only one study has so far have documented that participants with residual depressive symptoms in BD were less likely to report substance abuse. In this regard, the findings of the present study suggest the contrary and highlight the importance of identifying and managing comorbid conditions in BD as these were found to be associated with higher prevalence of residual depressive and manic symptoms.

The present study suggests significantly higher number of mean total episodes and higher number of mean manic episodes in those with only residual manic symptoms. This also suggests that those with higher number of manic episodes have higher manic residual symptoms and subsequently would be more functionally impaired. This finding is supported by previous studies which suggest that residual manic symptoms lead to manic, hypomanic, and mixed episodes’ recurrences frequently.

**Treatment correlates of residual symptoms in bipolar disorder**

In the present study, those with only residual depressive symptoms were more often receiving combination of mood stabilizers and antidepressants, suggesting that the use of antidepressants in patients with BD during the maintenance phase is influenced by the residual symptoms during the interepisodic phase. Further, it was also seen that those...
with residual symptoms of both types were more often prescribed combination of mood stabilizers, antipsychotics, and antidepressants and those with no residual symptoms were more often on mood stabilizer only prescriptions. More frequent use of antidepressants in those with both types of residual symptoms can be interpreted differently. It is quite possible that those patients actually have residual depressive symptoms to start with and the addition of antidepressants leads to some kinds of activation, which manifests as residual manic symptoms. It is also possible that those patients to start with have residual manic symptoms which lead to continuation of antipsychotics, which may possibly lead to emergence of depressive symptoms. These findings suggest that the pharmacotherapy in patients with BD not only should be tailored based on acute phase but also should also take into account the residual symptoms.

Another important finding of the study is that those with manic residual symptoms only were more often on combination of two mood stabilizers (lithium and valproate), probably suggesting that a subgroup of subjects with BD can be difficult to treat or have treatment-resistant mania and require combination of mood stabilizers. Available evidence suggests use of combination of mood stabilizers in cases of patients with treatment-resistant mania. Use of clozapine in treatment-refractory manic cases is well established; yet it lacks the regulatory approval for use in any phase of BD. In the present study too, clozapine was found to be more often used in those with manic residual symptoms when compared with other two groups with residual symptoms, possibly suggesting these to be treatment-refractory cases.

Limitations
The findings of the present study should be interpreted in accordance with the study limitations. First, it was a cross-sectional study limited to the treatment-seeking population attending to a tertiary care hospital. Second, we did not use any scales to evaluate the relationship between residual symptoms and functioning/outcome in subjects with BD as these are crucial parameters to ascertain the significance of residual symptoms. Third, psychiatric comorbidities in the study participants were not documented which could have also contribute to the prevalence of residual symptoms (such as hyperactivity or mood symptoms could be related to comorbid ADHD or residual anxiety symptoms could be related to comorbid anxiety disorder). Fourth, we did not evaluate the time to relapse to any polarity of episode due to any type of residual symptoms. This study also did not look at the association of residual symptoms with medications, as some of the residual symptoms may be actually the side effects of ongoing medications. Fifth, it is quite possible that, due to large sample size and lack of use of statistical correction for multiple corrections, some of the findings could have emerged as statistically significant and not necessarily suggests clinical significance. Finally, the documentation of residual symptoms was limited to HAM-D and YMRS. It is quite possible that there may be other symptoms, which are present during the interepisodic period, which are not evaluated by these scales. Future studies must attempt to address these issues.

CONCLUSIONS
Present exploratory study suggests that a substantial proportion of patients with BD have residual symptoms of both types. Presence of any comorbid physical illness and comorbid substance use disorder are associated with significantly higher residual depressive and manic symptoms. Most common depressive residual symptom includes psychic anxiety, and the most common manic residual symptom is lack of insight. Higher numbers of manic episodes per year of illness are associated with higher residual manic symptoms.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES
1. Angst J, Sellaro R. Historical perspectives and natural history of bipolar disorder. Biol Psychiatry 2000;48:445-57.
2. Gillin MJ, Swendsen J, Heller TL, Hammen C. Relapse and impairment in bipolar disorder. Am J Psychiatry 1995;152:1635-40.
3. Judd LL, Akiskal HS, Schettler PJ, Endicott J, Leon AC, Solomon DA, et al. Psychosocial disability in the course of bipolar I and II disorders: A prospective, comparative, longitudinal study. Arch Gen Psychiatry 2005;62:1322-30.
4. Judd LL, Akiskal HS, Schettler PJ, Coryell W, Endicott J, Maser JD, et al. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. Arch Gen Psychiatry 2003;60:261-9.
5. Samalin L, de Chazeron I, Vieta E, Bellivier F, Llorca PM. Residual symptoms and specific functional impairments in euthymic patients with bipolar disorder. Bipolar Disord 2016;18:164-73.
6. Alshuler LL, Post RM, Black DO, Keck PE Jr., Nolen WA, Frye MA, et al. Subsyndromal depressive symptoms are associated with functional impairment in patients with bipolar disorder: Results of a large, multisite study. J Clin Psychiatry 2006;67:1551-60.
7. Marangell LB. The importance of subsyndromal symptoms in bipolar disorder. J Clin Psychiatry 2004;65 Suppl 10:24-7.
8. Samalin L, Boyer L, Murr A, Pacchiarotti I, Reinares M, Bonnin CM, et al. Residual depressive symptoms, sleep disturbance and perceived cognitive impairment as determinants of functioning in patients with bipolar disorder. J Affect Disord 2017;210:280-6.
9. Meyer B. Residual mood symptoms and number of previous episodes predict recurrence of bipolar disorder. Evid Based Ment Health 2006;9:84.
10. Perlis RH, Ostacher MJ, Patel JK, Marangell LB, Zhang H, Wisniewski SR, et al. Predictors of recurrence in bipolar disorder: Primary outcomes from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Am J Psychiatry 2006;163:217-24.
11. Cretu JB, Culver JL, Goffin KC, Shah S, Ketter TA. Sleep, residual mood symptoms, and time to relapse in recovered patients with bipolar disorder. J Affect Disord 2016;190:162-6.
12. Belzeaux R, Correra N, Boyer L, Etain B, Loftus J, Bellivier F, et al. Depressive residual symptoms are associated with lower adherence to medication in bipolar patients without substance use disorder: Results from the FACE-BD cohort. J Affect Disord 2013;151:1009-15.
13. Goldberg JF, Perlis RH, Ghaemi SN, Calabrese JR, Bowden CL, Wisniewski S, et al. Adjunctive antidepressant use and symptomatic
