

Prevalence and association of comorbid substance dependence on the course and outcome of bipolar disorder: Findings from the bipolar disorder course and outcome study from India (BiD-CoIN study)

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ABSTRACT

Aim: To evaluate the prevalence of substance use disorder (SUD) and its association with the course and outcome of bipolar disorder (BD).

Materials and Methods: A total of 773 patients with BD were recruited from 14 centers in different parts of India, and they were evaluated for the prevalence of comorbid substance dependence, course and outcome, subjective cognitive functioning, and disability.

Results: About one-fourth (22.9%) of the participants had one or more substance dependence. In terms of specific substance of abuse, 136 (17.6%) had nicotine dependence, 80 (10.3%) patients had alcohol dependence, 13 (1.7%) had cannabis dependence, and nine (1.2%) had opioid dependence. Compared to those without comorbid substance dependence, those with a dual diagnosis (i.e., using at least one substance in a dependent pattern) were less educated, more often males, more often currently single, more often employed, had a lower number of depressive episodes per

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Submitted: 08-Aug-2021, **Revised:** 16-Jun-2022, **Accepted:** 27-Jul-2022, **Published:** 12-Oct-2022

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Access this article online	
Website: www.indianjpsychiatry.org	Quick Response Code 
DOI: 10.4103/indianjpsychiatry.indianjpsychiatry_665_21	

How to cite this article: Grover S, Avasthi A, Chakravarty R, Dan A, Chakraborty K, Neogi R, et al. Prevalence and association of comorbid substance dependence on the course and outcome of bipolar disorder: Findings from the bipolar disorder course and outcome study from India (BiD-CoIN study). Indian J Psychiatry 2022;64:449-56.

year of illness, had a higher number of manic and mixed episodes per year of illness in the first 5 years of illness, had a higher level of disability, and more often had a history of hospitalization and a history of receiving electroconvulsive therapy (ECT); also, a higher proportion of them had manic predominant polarity, more often had recurrent mania course, and were more often receiving a combination of lithium and valproate.

Conclusion: About one-fourth of BD patients have comorbid SUDs, and presence of SUD has a negative impact on the course and outcome of BD.

Key words: Bipolar disorder, comorbidity, course and outcome, substance use

INTRODUCTION

It is generally suggested that comorbid substance use disorders (SUDs) have a negative impact on the course and outcome of bipolar disorder (BD).^[1] Both the disorders are known to influence each other, that is, people with BD are considered to be more vulnerable to develop comorbid SUD and, on the other hand, available data suggest that patients with BD who have comorbid SUD have earlier age of onset of BD.^[1] In terms of epidemiology of SUD in patients with BD, many studies from the Western countries report the prevalence of SUD to be significantly high among patients with BD. The population-based studies suggest that the prevalence of SUD is as high as 61% in patients with BD-I and 48% among persons with BD-II. Clinic-based studies from different parts of the globe suggest that in patients with BD-I, the prevalence of alcohol abuse varies from 36% to 61.9%, opioid abuse from 4.6% to 8.5%, cannabis abuse from 19.7% to 36%, and cocaine abuse from 11.3% to 24.2%.^[2-10] In patients with BD-II, the prevalence of SUDs ranges from 22% to 38.9% for alcohol abuse, 5.6%–10% for cannabis abuse, 4% for cocaine abuse, and usually opioid abuse is not reported in people with BD-II.^[6,8]

Comorbid substance use in patients with BD has been reported to be associated with multiple negative consequences on the course of the BD, in the form of earlier or delayed onset of BD, delayed recovery from the episodes, especially depressive episodes, more frequent switches to mania, increased risk of suicidal behavior, poor medication adherence and poor quality of life, more functional impairment, legal problems, academic failures, treatment cost, and disability.^[4,11-19] In a meta-analysis of the available data, authors found that the risk of SUD in patients with BD is associated with male gender, higher number of manic episodes, and previous history of suicidality.^[1]

There is limited literature on dual diagnosis (DD; i.e., comorbid axis-I and SUD) from India. Multiple clinic-based studies which evaluated the prevalence of DD in patients attending drug deaddiction center or general hospital psychiatry clinics have reported the prevalence of DD to vary from 13.2% to 58%, with affective disorders accounting for a large proportion of cases across different

centers.^[20-24] Studies which have compared the prevalence of SUD in patients attending the outpatient services with healthy controls suggest that the prevalence of SUD is higher among patients attending the psychiatric outpatient services, compared to healthy controls. In patients with BD, nicotine use (33%) was the most common disorder, and this was followed by alcohol use (25%) and cannabis use (8%). However, this study included only 12 patients of BD.^[25] One study has specifically evaluated the quality of life of patients with DD and compared the same with that of those with patients with only BD and suggested that patients with DD have poor quality of life in all the domains.^[13]

Studies on BD in the Indian context, in general, exclude patients with DD, with occasional clinic-based studies reporting prevalence of comorbid SUD to be 27.7%–35%.^[26,27] In this background, this study aimed to evaluate the prevalence of SUD and its association with the course and outcome of BD.

MATERIALS AND METHODS

This multicentric study was carried out under the aegis of Research and Education Foundation subcommittee of the Indian Psychiatric Society. The study was conducted across 14 sites in different teaching hospitals in India. Ethics committees of all the institutes approved the study.

The primary aim of this study was to evaluate the long-term course and outcome of BD in patients with at least 10 years duration of illness. The outcomes were evaluated in terms of residual symptoms, insight, cognitive dysfunction, and disability. The study methodology and sample description, prescription pattern, and course and outcome have been published.^[28-31]

To be included in the study, participants were required to satisfy the criteria for diagnosis of BD as per the Diagnostic and Statistical Manual for Mental disorders, Fourth edition (DSM-IV), which were determined using the Mini International Neuropsychiatric Interview (MINI-PLUS).^[32] The participant should be a major (i.e., age ≥ 18 years), have illness duration of at least 10 years, currently be in clinical remission (i.e., Hamilton Depression Rating Scale [HDRS])^[33]

score of ≤ 7 and Young Mania Rating Scale [YMRS]^[34] score of ≤ 7), and be able to provide written informed consent to participate in the study. Those with evidence of organic brain syndrome, intellectual disability, organic mood disorder, and currently too sick to participate were excluded. MINI-plus was also used to evaluate the comorbid substance dependence. Insight was evaluated by using Insight scale for affective disorder (ISAD).^[35] Cognitive Functions were assessed by using cognitive complaints in bipolar disorder rating assessment (COBRA).^[36] Disability was assessed by using Indian Disability Evaluation Assessment Scale (IDEAS).^[37]

The National Institute of Mental Health- Retrospective Life Charts Method – Clinician and Self-rated versions (NIMH: LCM – P and S/R)^[38] was used to evaluate the course of illness. Affective morbidity was calculated by multiplying the number of episodes with duration of episodes in months and the severity of episodes (graded as: 1- mild, 2- moderate, 3- severe). Affective morbidity was computed for both polarities separately.

Statistical Package for Social Sciences, 14th edition (SPSS-14) was used to analyze the data. Mean and standard deviation, median, and range were computed for the continuous variables. Discontinuous variables are described in terms of frequency and percentages. Patients with and without comorbid substance dependence were compared by using the *t*-test, Mann–Whitney U test, Chi-square test, and Fischer exact test. *P* values less than 0.05 were considered significant.

RESULTS

The study included 773 participants, of whom 177 (22.9%) had one or more substance dependence. In terms of specific substance of abuse, 80 (10.3%) patients had alcohol dependence, 13 (1.7%) had cannabis dependence, nine (1.2%) had opioid dependence, and 136 (17.6%) had nicotine dependence. There was some variation across centers, with the prevalence of any substance dependence ranging from 0 to 57.1%, alcohol dependence from 0% to 32%, nicotine dependence from 0% to 54%, opioid dependence from 0% to 6.1%, and cannabis dependence from 0% to 12.7% [Supplementary Table 1].

Based on the presence or absence of at least one substance dependence, the study sample was divided into two groups, that is, those with no substance dependence ($n = 637$) and those with any of the SUDs, that is, the DD group ($n = 136$).

The mean age of the study sample was 45.66 (standard deviation [SD]: 10.5) years, and the mean duration of education was 10.3 (SD: 4.45) years. Male (63.6%) participants outnumbered females. Majority of the participants were married (82.7%), were on paid employment (65.7%), and Hindu (73.2%) by religion. Those from nuclear families (57.6%) and rural locality (53%) outnumbered those from non-nuclear

families and urban locality, respectively. In terms of income, the mean income of the patients was Rs. 24,463 (21,665; median: 18,000) at the time of the assessment [Table 1].

Compared to those without comorbid substance dependence, those with DD were less educated, more often males, more often currently single, and more often employed [Table 1].

In terms of clinical variables, compared to those without comorbid substance dependence, those with DD had lower number of depressive episodes in the lifetime, lower number of depressive episodes per year of illness, lower depressive affective morbidity index, higher number of manic episodes in the first 5 years of illness, higher number of manic episodes per year of illness in the first 5 years of illness, higher number of mixed episodes in their lifetime, and higher number of mixed episodes per year of illness. Additionally, compared to those without comorbid substance dependence, those with comorbid substance dependence had higher disability in all the domains [Table 2].

Further, compared to those without comorbid substance dependence, those with DD more often had mania as the first episode in their lifetime and the most recent episode, more often had history of hospitalization, history of receiving electroconvulsive therapy (ECT), higher proportion had manic predominant polarity, and more often had recurrent mania course [Table 3].

Medication history suggested that compared to those without comorbid substance dependence, higher proportion of those with DD were receiving a combination of mood stabilizer and antipsychotics, and lower proportion of them were receiving a combination of mood stabilizer, antipsychotics, antidepressants, and benzodiazepines. Those with DD were more often on haloperidol, carbamazepine, and a combination of lithium, valproate, and diazepam and were less often receiving sertraline and chlordiazepoxide [Table 3].

As very few females had SUD, we evaluated the data separately for males. Out of the 492 males, 127 (25.8%) had one or more substance dependence. In terms of specific substance of abuse, 78 (15.8%) had alcohol dependence, 13 (2.64%) had cannabis dependence, nine (1.8%) had opioid dependence, and 127 (25.8%) had nicotine dependence.

When the center-wise data was analyzed for males, the prevalence of alcohol dependence was found to range from 0% to 40.5, nicotine dependence from 0% to 81%, opioid dependence from 0% to 11.1%, and cannabis dependence from 0% to 19% [Supplementary Table 2].

Of the total 492 males, 127 had been using at least one substance in a dependent pattern. When similar comparisons were made for males only, compared to the whole sample,

Table 1: Comparison of sociodemographic profile of patients with and without substance dependence

	Whole sample (<i>n</i> =773), Mean (SD) [range]	BD without comorbid substance dependence, Mean (SD) [range]/ frequency (%) (<i>n</i> =637)	BD with comorbid substance dependence, Mean (SD) [range]/ frequency (%) (<i>n</i> =136)	<i>t</i> -test/Mann- Whitney U test/ Chi-square test (<i>P</i>)
Age (in years)	45.66 (10.50) [18-75]	45.51 (10.48) [18-72]	46.36 (10.58) [22-69]	-0.85 (0.39)
Years of education	10.30 (4.45) [0-21]	10.61 (4.29) [0-20]	8.90 (4.92) [0-21]	4.10 (<0.001***)
Patient's income in rupees	24,463 (21,665) [1000-100,000] Median 18,000	25,854 (21,950) [1000-100,000]	18,110 (19,087) [1000-100,000]	31,844 (<0.001***)
Gender				
Male	492 (63.6)	365 (57.3)	127 (93.4)	63.06 (<0.001***)
Female	281 (36.4)	272 (42.7)	9 (6.6)	
Marital status				
Currently single	134 (17.3)	101 (15.9)	33 (24.3)	5.53 (0.01**)
Currently married	639 (82.7)	536 (84.1)	103 (75.7)	
Occupation				
Unemployed and housewives	265 (34.3)	232 (36.4)	33 (24.3)	7.35 (0.007**)
Employed and earning	508 (65.7)	405 (63.6)	103 (75.7)	
Family type				
Nuclear	445 (57.6)	372 (58.4)	73 (53.7)	1.02 (0.31)
Non-nuclear	328 (42.4)	265 (41.6)	63 (46.3)	
Residence, <i>n</i> (%)				
Rural	410 (53.0)	340 (53.4)	70 (51.5)	0.16 (0.68)
Urban	363 (47.0)	297 (46.6)	66 (48.5)	
Religion, <i>n</i> (%)				
Hindus	566 (73.2)	455 (71.4)	111 (81.6)	5.93 (0.01**)
Non-Hindus	207 (26.8)	182 (28.6)	25 (18.4)	

BD=bipolar disorder, SD=standard deviation; ***P*≤0.01; ****P*≤0.001

besides showing significant difference in the same variables as noted in the whole sample, few more differences were noted. Among males, compared to those without comorbid substance dependence, males with DD were more often Hindu and did not differ significantly in terms of occupation. In terms of clinical variables, males with DD had longer duration of illness, higher prevalence of lifetime suicidal attempts, and lower prevalence of seeking faith-healing treatment; also, a higher proportion of them had disability above the benchmark, were more often receiving risperidone, chlorpromazine, clonazepam, and diazepam, and were less often receiving lithium [Supplementary Tables 3–5].

DISCUSSION

Our present study shows that about one-fourth (22.9%) of patients with BD have comorbid SUD, with comorbid nicotine dependence (17.6%) being the most common SUD, followed by alcohol dependence (10.3%), cannabis dependence (1.7%), and opioid dependence (1.2%). Among male participants, the prevalence of alcohol dependence was 15.8%, cannabis dependence was 2.64%, opioid dependence was 1.8%, and nicotine dependence was 25.8%. In the literature available from the Western countries, the prevalence of alcohol use disorders in subjects with BD has been reported to range from 36% to 61.9%; and the prevalence of opioid abuse ranges from 4.6% to 8.5%, cannabis abuse ranges from 19.7% to 36%, and cocaine abuse ranges from 11.3% to 24.2%.^[2-5,7-10] When we compare our findings with those of existing literature, it is evident that the prevalence of various SUDs is lower in Indian

patients with BD. This lower prevalence could be due to the fact that, in general, the prevalence of SUD in India is lower than in many of the Western countries. The National Mental Health Survey (NMHS), reported the prevalence of SUD to be 22.44% (confidence interval [CI]: 22.37–22.52), with nicotine use disorder being the most common (20.89%), alcohol use disorder being 4.65%, and other substances forming 0.57% of the total prevalence of SUD.^[39] The data from Western countries also suggest that the prevalence of alcohol use disorders in Europe and the USA varies from 10% to 16%.^[40] Accordingly, it can be said that lower prevalence of SUD in patients with BD from India, compared to that in Western countries, could be a general reflection of lower rates of SUD in India. Further, when we compare the findings of patients with BD to those of the NMHS, it is evident that, the prevalence of SUD other than nicotine in patients with BD is higher than that seen in the general population. In terms of nicotine dependence, the prevalence in the whole sample is slightly lower, but in males, the prevalence was comparable to the general population NMHS data. This high prevalence of SUD (other than nicotine) in patients with BD suggests that these patients require more attention, with focus on both the disorders.

When those with DD and only BD were compared in the whole sample, it was seen that patients with DD were older, less educated, more often males, more often currently single, and more often employed. The higher prevalence of SUD in males is in consonance with the national data for SUD in the general population from India^[39] and the data from Western countries, which have evaluated SUD in patients with BD.^[1]

Table 2: Comparison of continuous clinical variables of those with and without comorbid substance dependence

Variables	Whole sample, Mean (SD) [range]/n (%) (n=773)	Median [range]	BD without comorbid substance dependence, Mean (SD) [range]/ frequency (%) (n=637)	BD with comorbid substance dependence, Mean (SD)/ frequency (%) (n=136)	t-test/Mann- Whitney U test/ Chi-square test (P)
Age of onset (years)	26.30 (8.54)	25 [9-55]	26.15 (8.49)	26.98 (8.79)	-1.02 (0.30)
Duration of illness (months)	232.05 (94.55)	216 [4-660]	230.08 (92.64)	241.30 (102.8)	-1.25 (0.31)
Time spent in episodes (months)	27.24 (30.13)	18 [3-280]	26.96 (31.07)	28.54 (25.35)	39,432 (0.10)
Mean number of total episodes in the lifetime	8.58 (10.60)	6 [1-140]	8.57 (11.01)	8.63 (8.45)	43,117 (0.93)
Mean number of total episodes per year of illness	0.49 (0.74)	0.30 [0.4-14]	0.50 (0.78)	0.46 (0.53)	41,413 (0.42)
Mean number of total episodes in the first 5 years	2.39 (3.35)	2 [0-70]	2.35 (3.42)	2.60 (3.03)	40,292 (0.19)
Mean number of total episodes per year of illness in the first 5 years	0.47 (0.67)	0.4 [0-14]	0.47 (0.68)	0.52 (0.60)	40,292 (0.19)
Duration of current remission (months)	32.84 (50.04)	12 [1-348]	32.49 (48.81)	34.51 (55.59)	42,940 (0.87)
Mean number of depressive episodes in the lifetime	3.36 (5.51)	2 [0-70]	3.47 (5.73)	2.83 (4.28)	36,621 (0.004**)
Mean number of depressive episodes per year of illness	0.19 (0.39)	0.11 [0-7]	0.20 (0.40)	0.15 (0.29)	34,857 (<0.001***)
Mean number of depressive episodes in the first 5 years	0.99 (1.86)	1 [0-35]	0.97 (1.81)	1.07 (2.08)	41,275 (0.35)
Mean number of depressive episodes per year of illness in the first 5 years	0.19 (0.37)	0.2 [0-7]	0.19 (0.36)	0.21 (0.41)	41,275 (0.35)
Time spent in depression (months)	2.43 (1.13)	3 [0-4]	2.45 (1.12)	2.35 (1.19)	0.870 (0.38)
Average severity of depressive episodes	1.87 (0.80)	2 [0-3]	1.88 (0.79)	1.79 (0.81)	1.23 (0.21)
Affective morbidity index- depressive	17.59 (26.47)		18.55 (27.08)	13.06 (22.93)	33,499 (<0.001***)
Mean number of manic episodes in the lifetime	3.68 (4.75)	2 [0-50]	3.57 (4.63)	4.21 (5.29)	38,835 (0.05*)
Mean number of manic episodes per year of illness	0.21 (0.30)	0.13 [0-5]	0.20 (0.30)	0.22 (0.27)	39,672 (0.12)
Mean number of manic episodes in the first 5 years	1.17 (1.66)	1 [0-25]	1.11 (1.62)	1.46 (1.83)	36,769 (0.003**)
Mean number of manic episodes per year of illness in the first 5 years	0.23 (0.33)	0.2 [0-5]	0.22 (0.32)	0.29 (0.36)	36,769 (0.003**)
Time spent in mania/hypomania/mixed (months)	3.29 (3.67)	2 [1-50]	3.38 (3.95)	2.87 (1.80)	41,261 (0.37)
Average severity of manic/hypomanic/mixed episodes	2.19 (0.40)	2 [1-3]	2.20 (0.40)	2.16 (0.40)	0.83 (0.40)
Affective morbidity index manic	27.11 (68.46)		28.03 (74.20)	22.78 (29.00)	41,355 (0.40)
Mean number of hypomanic episodes in the lifetime	0.81 (2.97)	0 [0-50]	0.86 (3.21)	0.58 (1.35)	42,630 (0.71)
Mean number of hypomanic episodes per year of illness	0.04 (0.19)	0 [0-3]	0.05 (0.21)	0.02 (0.07)	43,120 (0.91)
Mean number of hypomanic episodes in the first 5 years	0.12 (0.60)	0 [0-10]	0.14 (0.64)	0.05 (0.31)	41,404 (0.08)
Mean number of hypomanic episodes per year of illness in the first 5 years	0.02 (0.12)	0 [0-2]	0.02 (0.07)	0.01 (0.06)	41,404 (0.08)
Mean number of mixed episodes in the lifetime	0.22 (1.52)	0 [0-40]	0.22 (1.65)	0.26 (0.59)	39,712 (0.007**)
Mean number of mixed episodes per year of illness	0.0115 (0.05111)	0 [0-1]	0.01 (0.05)	0.01 (0.03)	39,811 (0.009**)
Mean number of mixed episodes in the first 5 years	0.041 (0.229)	0 [0-3]	0.04 (0.23)	0.04 (0.20)	42,910 (0.59)
Mean number of mixed episodes per year of illness in the first 5 years	0.008 (0.045)	0 [0-0.6]	0.008 (0.046)	0.008 (0.041)	42,910 (0.59)
Daily dosage of lithium	799.58 (211.42)	900 [300-1350]	804 (212)	768 (208)	1.13 (0.25)
Daily dose of valproate	932.71 (349.84)	1000 [200-2000]	950 (354)	868 (327)	1.94 (0.05)
Total COBRA score	9.79 (6.99)	9 [0-40]	9.85 (7.02)	9.50 (6.83)	0.53 (0.59)
ISAD total	34.23 (33.69)	21 [0-85]	23.15 (20.68)	23.63 (22.53)	-0.24 (0.80)
IDEAS domain scores					
Self-care	0.25 (0.53)	0 [0-3]	0.22 (0.50)	0.35 (0.62)	39,139 (0.01***)
Interpersonal relations	0.42 (0.65)	0 [0-3]	0.40 (0.64)	0.53 (0.66)	38,325 (0.01**)
Communication and understanding	0.34 (0.62)	0 [0-3]	0.34 (0.63)	0.34 (0.54)	42,050 (0.48)
Work	0.64 (0.88)	0 [0-4]	0.58 (0.85)	0.90 (0.95)	34,124 (<0.001***)
Total IDEAS score	1.64 (2.22)	1 [0-12]	1.54 (2.21)	2.12 (2.22)	35,395 (<0.001***)
IDEAS global score	5.64 (2.22)	[4-16]	5.54 (2.21)	6.12 (2.22)	-2.79 (0.005**)

BD=bipolar disorder, HDRS=Hamilton Depression Rating Scale, SD=standard deviation, YMRS=Young Mania Rating Scale, COBRA: Cognitive Complaints In Bipolar Disorder Rating Assessment; IDEAS: Indian Disability Evaluation Assessment Scale; ISAD: Insight scale for affective disorder. *P≤0.05; **P≤0.01; ***P≤0.001

Previous studies have also reported the negative impact of comorbid SUD on the educational status of patients with BD.^[41,42] Patients of DD being more often employed may be actually a reflection of higher proportion of males in this sample, who are traditionally involved in paid job in the Indian context, and is in consonance with previous studies

which have evaluated the gender differences in patients with BD.^[43] In terms of clinical variables, compared to those without comorbid substance dependence, those with DD spent more time in the episodes. This finding suggests that comorbid SUD possibly leads to delayed recovery from the episodes, as has been reported in some of the earlier

Table 3: Comparison of categorical clinical variables of those with and without comorbid substance dependence

Clinical variables	Whole sample, Mean (SD) [range]/n (%) (n=773)	BD without comorbid substance dependence, Mean (SD)/frequency (%) (n=637)	BD with comorbid substance dependence, Mean (SD)/frequency (%) (n=136)	t-test/Mann- Whitney U test/ Chi-square test (P)
Diagnosis				
BD type I	714 (92.37)	587 (92.2)	127 (93.4)	0.24 (0.62)
BD type II	59 (7.63)	50 (7.8)	9 (6.6)	
Nature of first episode				
Manic/hypomanic	449 (58.1)	357 (56.0)	92 (67.6)	6.19 (0.01**)
Depressive	324 (41.9)	280 (44.0)	44 (32.4)	
Polarity of most recent episode				
Depression	323 (41.8)	282 (44.3)	41 (30.1)	16.62 (0.001**)
Mania/hypomania/mixed	450 (58.2)	355 (55.7)	95 (69.9)	
Lifetime suicidal attempts	242 (31.3)	191 (29.9)	51 (37.5)	2.94 (0.08)
Lifetime history of breakthrough episodes	282 (36.4)	242 (37.9)	40 (29.4)	3.43 (0.06)
Lifetime history of seasonality	73 (9.44)	63 (9.9)	10 (7.4)	0.84 (0.35)
Lifetime history of rapid cycling affective disorder	45 (5.8)	40 (6.2)	5 (3.7)	1.38 (0.23)
Lifetime history of faith-healing treatment	671 (86.7)	558 (87.6)	113 (83.1)	1.83 (0.17)
Lifetime history of mood stabilizer prophylaxis	770 (99.5)	634 (99.5)	136 (100.0)	FE=0.46
Lifetime history of discontinuing prophylaxis on their own	712 (92.0)	585 (91.8)	127 (93.4)	0.44 (0.50)
Number of patients with history of relapse due to poor medication adherence	505 (65.2)	415 (65.1)	90 (66.2)	0.06 (0.79)
Any history of hospitalization	402 (51.9)	311 (48.8)	91 (66.9)	14.69 (<0.001***)
Any history of electroconvulsive therapy	183 (23.6)	133 (20.9)	50 (36.8)	15.65 (<0.001***)
Obesity [#]	457 (59.0)	384 (60.3)	73 (53.7)	1.92 (0.16)
Cognitive impairment present as per COBRA	322 (41.6)	264 (41.4)	58 (42.6)	0.06 (0.79)
Total number of lifetime episodes				
<2	4 (0.6)	4 (0.6)	0	1.45 (0.69)
2-5	338 (48.9)	308 (48.4)	68 (50.0)	
5-10	209 (30.2)	197 (30.9)	38 (27.9)	
>10	140 (20.3)	128 (20.1)	30 (22.1)	
Predominant polarity (Harvard definition- with mixed)				
Depressive	226 (29.2)	192 (30.1)	34 (25.0)	5.52 (0.06)
Mania/hypomania/mixed	457 (59.1)	365 (57.3)	92 (67.6)	
Indeterminate	90 (11.6)	80 (12.6)	10 (7.4)	
Predominant polarity (Harvard definition- without mixed)				
Depressive	244 (31.6)	209 (32.8)	35 (25.7)	5.93 (0.05)
Mania/hypomania	434 (56.1)	345 (54.2)	89 (65.4)	
Indeterminate	95 (12.3)	83 (13.0)	12 (8.8)	
Predominant polarity (Barcelona definition)				
Depressive	159 (20.6)	137 (21.5)	22 (16.2)	11.32 (0.003**)
Mania/hypomania	354 (45.8)	274 (43.0)	80 (58.8)	
Not determined	260 (33.6)	226 (35.5)	34 (25.0)	
Recurrent/unipolar mania				
≥2 episodes of mania without depression	115 (14.9)	81 (12.7)	34 (25.0)	13.54 (<0.001***)
At least one lifetime episode with psychotic symptoms	326 (42.2)	249 (39.1)	77 (56.6)	14.11 (<0.001***)
Disability ≥40%	142 (18.4)	135 (21.2)	42 (30.8)	8.59 (0.003**)
Treatment				
MS + AP	200 (38.3)	156 (24.4)	44 (32.4)	6.55 (0.01**)
MS + AD	29 (13.2)	26 (4.1)	3 (2.2)	0.63 (0.42)
MS + AD + AP	51 (20.4)	47 (7.4)	4 (2.9)	1.97 (0.16)
MS only	119 (21.7)	99 (15.5)	20 (14.7)	0.16 (0.68)
AP only	9 (1.7)	9 (1.4)	0	1.43 (0.47)
AP + AD	4 (1.0)	2 (0.3)	2 (1.5)	FE=0.356
MS + AP + BZD	100 (12.9)	69 (10.8)	31 (22.8)	2.96 (0.08)
MS + AD + BZD	73 (9.4)	65 (10.2)	8 (5.9)	3.38 (0.06)
MS + AD + AP + BZD	108 (13.9)	100 (15.7)	8 (5.9)	9.86 (0.002**)
MS + BZD	49 (6.3)	41 (6.4)	8 (5.9)	0.24 (0.62)
AP + BZD	4 (0.5)	4 (0.4)	0	FE=1.000
AP + AD + BZD	4 (0.5)	3 (0.5)	1 (0.7)	FE=0.444
APs				
Olanzapine	245 (31.7)	202 (31.7)	43 (31.6)	0.00 (0.98)
Risperidone	74 (9.6)	54 (8.5)	20 (14.7)	5.02 (0.02*)
Quetiapine	86 (11.1)	70 (10.9)	16 (11.8)	0.06 (0.79)

Contd...

Table 3: Contd...

Clinical variables	Whole sample, Mean (SD) [range]/n (%) (n=773)	BD without comorbid substance dependence, Mean (SD)/frequency (%) (n=637)	BD with comorbid substance dependence, Mean (SD)/frequency (%) (n=136)	t-test/Mann- Whitney U test/ Chi-square test (P)
Aripiprazole	26 (2.4)	22 (3.5)	4 (2.9)	0.09 (0.76)
Lurasidone	13 (1.7)	10 (1.6)	3 (2.2)	0.27 (0.60)
Haloperidol	22 (2.8)	12 (1.9)	10 (7.4)	12.12 (<0.001***)
Chlorpromazine	17 (2.2)	12 (2.0)	5 (3.7)	1.67 (0.19)
ADs				
Escitalopram	38 (4.9)	33 (5.2)	5 (3.7)	0.54 (0.46)
Sertraline	175 (22.6)	171 (26.8)	4 (2.9)	36.56 (<0.001***)
Fluoxetine	31 (4.0)	26 (4.1)	5 (3.7)	0.04 (0.82)
Paroxetine	3 (0.4)	1 (0.2)	2 (1.5)	FE=0.08
Venlafaxine	9 (1.2)	9 (1.4)	0	1.94 (0.16)
Bupropion	10 (1.3)	8 (1.3)	2 (1.5)	0.04 (1.00)
MSs				
Lithium	301 (38.9)	280 (43.9)	21 (15.4)	15.69 (0.009**)
Valproate	342 (44.2)	274 (43.0)	68 (50.0)	2.21 (0.13)
Carbamazepine	16 (2.1)	8 (1.3)	8 (5.9)	11.83 (0.001***)
Lithium + valproate	57 (7.4)	37 (5.8)	20 (14.7)	12.99 (<0.001***)
Lamotrigine	13 (1.7)	13 (2.0)	0	2.82 (0.18)
BZDs				
Clonazepam	112 (14.5)	86 (13.5)	26 (19.1)	2.85 (0.09)
Diazepam	39 (5.0)	21 (3.3)	18 (13.2)	23.10 (<0.001***)
Lorazepam	44 (5.7)	36 (5.7)	8 (5.9)	0.01 (0.91)
Chlordiazepoxide	139 (18.0)	136 (21.4)	3 (2.2)	27.85 (<0.001***)
Etizolam	4 (0.5)	4 (0.6)	0	FE=0.62

AD=antidepressant, AP=antipsychotics, BD=bipolar disorder, BZD=benzodiazepines, MS=mood stabilizer, SD=standard deviation. #: Defined based on Body Mass Index of >25 kilogram/meter²; FE= Fischer Exact Test Value; *P≤0.05; **P≤0.01; ***P≤0.001

studies.^[5] In the present study, patients with DD had less severe depressive episodes, lower depressive affective morbidity index, higher number of manic episodes, higher number of manic episodes per year of illness in the first 5 years of illness, and more often had recurrent mania course. Similar findings were noted when the analysis was limited only to males. The higher prevalence of SUD in patients with BD-I in the whole sample is in line with the existing literature.

An important finding of the present study is the negative impact of SUD on the cognitive functioning of patients with BD. In general, previous studies which have evaluated cognitive impairment in patients of BD too suggest that comorbid SUDs have a negative impact.^[44] This finding suggests that clinicians dealing with DD with BD as one of the diagnosis should psychoeducate the patients about such an association and must aim to achieve abstinence from the SUD to improve the outcome of BD. Compared to those with BD only, patients with DD were more often on psychotropic medications and a higher proportion of them were prescribed a combination of lithium and valproate, which possibly reflect higher severity of the illness. These findings again suggest the importance of achieving complete abstinence in patients with BD.

The present study has certain limitations which must be kept in mind. The study did not evaluate the exact age of onset of SUD, severity of SUD, personality characteristics, and

features like impulsivity, which can also influence the overall outcome in patients with BD. The study also did not evaluate other clinical characteristics such as family history of SUD, BD, or DD. Neither it evaluated other psychosocial outcomes such as quality of life, current medication adherence, and type of treatment received over the years, which can influence the course and outcome of BD and DD. Finally, this was a cross-sectional study; hence, a cause-effect relationship between SUD and BD could not be assessed. Future studies should attempt to overcome these limitations.

To conclude, the present study suggests that about one-fourth of patients with BD have comorbid SUD, with nicotine dependence being the most common, followed by alcohol, cannabis, and opioids. The proportion of males having SUD is higher, with prevalence of nicotine dependence being 25.8%, alcohol dependence being 15.8%, cannabis dependence being 2.64%, and opioid dependence being 1.8%. People with DD have lower educational attainment, more number of manic episodes, higher level of cognitive impairment, and more often require use of combination of medications. Hence, clinicians managing DD with BD as one of the disorders should focus on both the disorders together and must aim to achieve abstinence from SUD to reduce the negative consequences of SUD on BD.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. The patients understand that due

efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Prevalence of substance use disorders across different centers

Name	Total (n=773)	SUD (n=177)	Alcohol (n=80)	Nicotine (n=136)	Opioid (n=9)	Cannabis (n=13)
All India Institute of Medical Sciences, Jodhpur	49 (6.3)	13 (26.5)	2 (4.1)	11 (22.4)	3 (6.1)	0
All India Institute of Medical Sciences, New Delhi	50 (6.4)	10 (20)	3 (6)	7 (14)	1 (2)	2 (4)
Ahmedabad Municipal Corporation Medical Education Trust Medical College, Ahmedabad	25 (3.2)	2 (8)	1 (4)	0	1 (4)	0
Burdwan Medical College, Burdwan	63 (8.1)	36 (57.1)	17 (27)	34 (54)	1 (1.6)	8 (12.7)
College of Medicine and J.N.M. Hospital WBUHS, Kalyani, Kolkata	58 (7.5)	16 (27.6)	11 (19)	7 (12)	0	0
Kasturba Medical College, Manipal	52 (6.7)	17 (32.7)	7 (13.5)	14 (27)	0	0
R G Kar Medical College, Kolkata	58 (7.5)	0	0	0	0	0
Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry	51 (6.5)	13 (25.5)	7 (13.7)	9 (17.6)	0	0
Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Ambala	50 (6.4)	24 (48)	16 (32)	17 (34)	0	0
Murshidabad Medical College and Hospital, Murshidabad	21 (2.7)	1 (4.8)	1 (4.7)	1 (4.7)	0	0
Topiwala National Medical College (Nair Hospital), Mumbai	50 (6.4)	20 (40%)	3 (6)	18 (36)	1 (2)	1 (2)
Post Graduate Institute of Medical Education and Research, Chandigarh	92 (11.9)	20 (21.7)	11 (12)	14 (15.2)	2 (2.2)	1 (1.1)
Lokmanya Tilak Municipal General Hospital (SION Hospital), Mumbai	107 (13.8)	0	0	0	0	0
Silchar Medical College, Silchar	47 (6.1)	5 (10.6)	1 (2.1)	1 (2.1)	0	1 (2.1)

For the percentages in the parenthesis in column 2 to 6, the denominator is the sample size for the particular center

Supplementary Table 2: Prevalence of substance use disorders in males across different centers

Name	Total (n=492)	SUD (n=127)	Alcohol (n=78)	Nicotine (n=127)	Opioid (n=9)	Cannabis (n=13)
All India Institute of Medical Sciences, Jodhpur	27 (5.5)	9 (33.3)	2 (7.4)	7 (25.9)	3 (11.1)	0
All India Institute of Medical Sciences, New Delhi	32 (6.5)	10 (31.2)	3 (9.4)	7 (31.9)	1 (3.1)	2 (6.2)
Ahmedabad Municipal Corporation Medical Education Trust Medical College, Ahmedabad	13 (2.6)	2 (15.4)	1 (7.7)	0	1 (7.7)	0
Burdwan Medical College, Burdwan	42 (8.5)	36 (85.7)	17 (40.5)	34 (81)	1 (2.4)	8 (19.0)
College of Medicine and J.N.M. Hospital WBUHS, Kalyani, Kolkata	37 (7.5)	15 (40.5)	10 (27)	7 (18.9)	0	0
Kasturba Medical College, Manipal	34 (6.9)	16 (47)	7 (20.6)	14 (41.2)	0	0
R G Kar Medical College, Kolkata	36 (7.3)	0	0	0	0	0
Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry	22 (4.4)	12 (54.5)	7 (31.8)	8 (36.4)	0	0
Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Ambala	32 (6.5)	21 (65.2)	15 (46.8)	15 (46.8)	0	0
Murshidabad Medical College and Hospital, Murshidabad	13 (2.6)	1 (7.7)	1 (7.7)	1 (7.7)	0	0
Topiwala National Medical College (Nair Hospital), Mumbai	30 (6.0)	18 (60)	3 (10)	16 (53.3)	1 (3.33)	1 (3.3)
Post Graduate Institute of Medical Education and Research, Chandigarh	65 (13.2)	20 (30.8)	11 (16.9)	14 (21.5)	2 (3.1)	1 (1.53)
Lokmanya Tilak Municipal General Hospital (SION Hospital), Mumbai	79 (16.0)	0	0	0	0	0
Silchar Medical College, Silchar	30 (6.0)	5 (16.7)	1 (3.3)	4 (13.3)	0	1 (3.3)

For the percentages in the parenthesis in column 2 to 6, the denominator is the sample size for the particular center

Supplementary Table 3: Comparison of sociodemographic profile of patients with and without substance dependence among males

	Whole sample (n=492)	BD without comorbid substance dependence, Mean (SD)/frequency (%) (n=365)	BD with comorbid substance dependence, Mean (SD)/ frequency (%) (n=127)	t-test/Mann- Whitney U test/ Chi-square test (P)
Age (in years)	46.18 (10.70)	46.21 (10.73)	46.09 (10.67)	-0.85 (0.39)
Years of education	10.75 (4.19)	11.31 (3.79)	9.14 (4.84)	4.10 (<0.001***)
Patient's income in rupees	24,247 (20,806)	26,784 (21,445)	16,956 (16,912)	4.68 (<0.001***)
Marital status				
Currently single	78	47 (12.9)	31 (25.2)	9.39 (0.002**)
Currently married	414	318 (87.1)	96 (74.8)	
Occupation				
Unemployed	72 (14.6)	47 (12.9)	25 (19.7)	3.49 (0.06)
Employed and earning	420 (85.4)	318 (87.1)	102 (80.3)	
Family type				
Nuclear	263 (53.5)	196 (53.7)	67 (52.8)	1.02 (0.31)
Non-nuclear	229 (66.9)	169 (46.3)	60 (47.2)	
Residence- n (%)				
Rural	268 (54.5)	202 (55.3)	66 (51.9)	0.32 (0.51)
Urban	224 (45.5)	163 (44.7)	61 (48.1)	
Religion- n (%)				
Hindus	370 (75.2)	264 (72.3)	106 (82.7)	6.26 (0.01*)
Non-Hindus	122 (24.8)	101 (26.7)	21 (17.3)	

BD=bipolar disorder, SD=standard deviation; *P≤0.05; **P≤0.01; ***P≤0.001 1

Supplementary Table 4: Comparison of clinical variables of male patients with and without comorbid substance dependence

Variables	Whole male sample, Mean (SD) [range]/n (%) (n=492)	Median [range]	BD without comorbid substance dependence, Mean (SD)/frequency (%) (n=365)	BD with comorbid substance dependence, Mean (SD)/frequency (%) (n=127)	t-test/Mann-Whitney U test/Chi-square test (P)
Age of onset (years)	26.71 (8.8)	25 [9-55]	26.66 (8.80)	26.84 (8.77)	1.01 (0.92)
Duration of illness (months)	232.65 (97.00)	216 [4-660]	231.39 (92.54)	241.11 (92.54)	5.14 (<0.001***)
Time spent in episodes (months)	27.21 (28.52)	18 [3-280]	26.67 (29.41)	28.76 (25.82)	21,047 (0.12)
Mean number of total episodes in the lifetime	8.85 (11.63)	6 [1-140]	8.95 (12.51)	8.56 (8.62)	22,482 (0.61)
Mean number of total episodes per year of illness	0.043 (0.073)	0.30 [0.4-14]	0.54 (0.97)	0.46 (0.55)	21,370 (0.19)
Mean number of total episodes in the first 5 years	2.45 (3.88)	2 [0-70]	2.39 (4.11)	2.63 (3.13)	21,284 (0.15)
Mean number of total episodes per year of illness in the first 5 years	0.491 (0.777)	0.4 [0-14]	0.47 (0.82)	0.52 (0.62)	21,284 (0.15)
Duration of current remission (months)	32.35 (48.85)	12 [1-348]	31.42 (45.90)	35.05 (56.60)	22,711 (0.73)
Mean number of depressive episodes in the lifetime	3.45 (5.98)	2 [0-70]	3.63 (6.43)	2.94 (4.39)	19,554 (0.008**)
Mean number of depressive episodes per year of illness	0.208 (0.172)	0.11 [0-7]	0.22 (0.49)	0.16 (0.30)	18,519 (0.001**)
Mean number of depressive episodes in the first 5 years	1.05 (2.14)	1 [0-35]	1.03 (2.14)	1.09 (2.14)	21,604 (0.22)
Mean number of depressive episodes per year of illness in the first 5 years	0.209 (0.428)	0.2 [0-7]	0.20 (0.42)	0.21 (0.42)	21,604 (0.22)
Time spent in depression (months)	2.45 (1.15)	3 [0-4]	2.48 (1.13)	2.37 (1.20)	0.89 (0.37)
Average severity of depressive episodes	1.86 (0.81)	2 [0-3]	1.89 (0.81)	1.78 (0.81)	1.38 (0.16)
Affective morbidity index-depressive	17.42 (25.43)		18.77 (25.96)	13.56 (23.53)	17,833 (<0.001***)
Mean number of manic episodes in the lifetime	3.87 (5.24)	2 [0-50]	3.77 (5.21)	4.14 (5.35)	21,364 (0.18)
Mean number of manic episodes per year of illness	0.218 (0.331)	0.13 [0-5]	0.21 (0.34)	0.21 (0.27)	21,931 (0.36)
Mean number of manic episodes in the first 5 years	1.24 (1.87)	1 [0-25]	1.15 (1.87)	1.50 (1.88)	19,409 (0.36)
Mean number of manic episodes per year of illness in the first 5 years	0.248 (0.375)	0.2 [0-5]	0.23 (0.37)	0.30 (0.37)	19,409 (0.36)
Time spent in mania/hypomania/mixed episodes (months)	3.49 (4.04)	2 [1-50]	3.68 (4.55)	2.94 (1.83)	22,994 (0.89)
Average severity of manic/hypomanic/mixed episodes	2.20 (0.41)	2 [1-3]	2.21 (0.41)	2.17 (0.41)	0.95 (0.33)
Affective morbidity index- manic	28.74 (70.42)		30.72 (80.19)	23.05 (29.64)	23,211 (0.40)
Mean number of hypomanic episodes in the lifetime	0.87 (3.21)	0 [0-50]	0.98 (3.64)	0.57 (1.33)	23,118 (0.95)
Mean number of hypomanic episodes per year of illness	0.054 (0.232)	0 [0-3]	0.06 (0.26)	0.02 (0.07)	23,096 (0.94)
Mean number of hypomanic episodes in the first 5 years	0.128 (0.636)	0 [0-10]	0.15 (0.71)	0.05 (0.71)	21,898 (0.06)
Mean number of hypomanic episodes per year of illness in the first 5 years	0.025 (0.127)	0 [0-2]	0.03 (0.14)	0.01 (0.06)	21,898 (0.06)
Mean number of mixed episodes in the lifetime	0.14 (0.47)	0 [0-40]	0.09 (0.41)	0.27 (0.61)	20,249 (<0.000***)
Mean number of mixed episodes per year of illness	0.007 (0.027)	0 [0-1]	0.005 (0.02)	0.01 (0.03)	20,295 (<0.000***)
Mean number of mixed episodes in the first 5 years	0.036 (0.198)	0 [0-3]	0.03 (0.19)	0.04 (0.21)	22,784 (0.36)
Mean number of mixed episodes per year of illness in the first 5 years	0.007 (0.039)	0 [0-0.6]	0.006 (0.03)	0.009 (0.04)	22,784 (0.36)
Daily dosage of lithium	811.88 (214.88)	900 [300-1350]	804 (212)	768 (208)	1.13 (0.25)
Daily dose of valproate	929.66 (343.05)	1000 [200-2000]	950 (354)	868 (327)	1.94 (0.05)
Total COBRA score	9.79 (6.99)	9 [0-40]	10.08 (6.93)	9.56 (6.62)	0.73 (0.46)
ISAD total	34.23 (33.69)	21 [0-85]	23.73 (20.84)	22.75 (21.50)	0.44 (0.65)
IDEAS domain scores					
Self-care	0.25 (0.53)	0 [0-3]	0.22 (0.52)	0.37 (0.64)	20,489 (0.006**)
Interpersonal relations	0.42 (0.65)	0 [0-3]	0.39 (0.65)	0.55 (0.66)	19,653 (0.002**)
Communication and understanding	0.34 (0.62)	0 [0-3]	0.34 (0.65)	0.35 (0.55)	22,230 (0.37)
Work	0.64 (0.88)	0 [0-4]	0.57 (0.88)	0.95 (0.96)	17,223 (<0.000***)
Total IDEAS score	1.64 (2.22)	1 [0-12]	1.52 (2.35)	2.22 (2.22)	17,663 (<0.000***)
IDEAS global score	5.64 (2.22)	[4-16]	5.51 (2.35)	6.22 (2.22)	-2.96 (0.003**)

BD=bipolar disorder, HDRS=Hamilton Depression Rating Scale, SD=standard deviation, YMRS=Young Mania Rating Scale, COBRA: Cognitive Complaints In Bipolar Disorder Rating Assessment ; IDEAS: Indian Disability Evaluation Assessment Scale; ISAD: Insight scale for affective disorder. **P≤0.01; ***P≤0.001

Supplementary Table 5: Comparison of clinical variables of male patients with and without comorbid substance dependence

Clinical variables	Whole male sample, Mean (SD)/n (%) (n=492)	BD without comorbid substance dependence, Mean (SD)/frequency (%) (n=365)	BD with comorbid substance dependence, Mean (SD)/frequency (%) (n=127)	t-test/Mann-Whitney U test/Chi-square test (P)
Diagnosis				
BD type I	453 (92.1)	334 (91.5)	119 (93.7)	0.62 (0.43)
BD type II	39 (7.9)	31 (8.5)	8 (6.3)	
Nature of first episode				
Manic/hypomanic	293 (59.6)	206 (56.4)	87 (68.5)	5.69 (0.01**)
Depressive	199 (40.4)	159 (43.6)	40 (31.5)	
Polarity of most recent episode				
Depression	207 (42.1)	170 (46.6)	37 (29.1)	11.76 (0.001**)
Mania/hypomania/mixed	285 (57.9)	195 (53.4)	90 (70.9)	
Lifetime suicidal attempts	138 (28.0)	89 (24.4)	49 (38.6)	9.41 (0.002**)
Lifetime history of breakthrough episodes	182 (36.9)	144 (39.5)	38 (29.9)	3.67 (0.05)
Lifetime history of seasonality	44 (8.9)	35 (9.6)	9 (7.1)	0.72 (0.39)
Lifetime history of Rapid Cycling Affective Disorder	25 (5.1)	20 (5.5)	5 (3.9)	0.46 (0.49)
Lifetime history of faith-healing treatment	435 (88.4)	331 (90.7)	104 (81.9)	7.11 (0.008**)
Lifetime history of MS prophylaxis	490 (99.6)	363 (99.5)	127 (100.0)	FE=0.55
Lifetime history of discontinuing prophylaxis on their own	452 (91.9)	333 (91.2)	119 (93.7)	0.76 (0.38)
Number of patients with history of relapse due to poor medication adherence	331 (67.3)	245 (67.1)	86 (67.7)	0.01 (0.90)
Any history of hospitalization	249 (50.6)	163 (44.7)	86 (67.7)	20.04 (<0.001***)
Any history of electroconvulsive therapy	117 (23.8)	72 (19.7)	45 (35.4)	12.82 (<0.001***)
Obesity [#]	262 (53.3)	192 (52.6)	70 (55.1)	0.23 (0.62)
Cognitive impairment present as per COBRA	211 ()	156 (42.7)	55 (43.3)	0.01 (0.91)
Total number of lifetime episodes				
<2	2 (0.4)	2 (0.5)	0	1.32 (0.72)
2-5	242 (49.1)	176 (48.2)	66 (51.9)	
5-10	148 (30.0)	113 (30.9)	35 (27.6)	
>10	100 (20.3)	74 (20.3)	26 (20.5)	
Predominant polarity (Harvard definition- with mixed)				
Depressive	142 (28.8)	108 (29.6)	33 (25.9)	2.87 (0.23)
Mania/hypomania/mixed	297 (60.3)	213 (58.4)	84 (66.1)	
Indeterminate	54 (10.9)	44 (12.1)	10 (7.9)	
Predominant polarity (Harvard definition- without mixed)				
Depressive	148 (30.0)	114 (31.2)	34 (26.8)	3.26 (0.19)
Mania/hypomania	286 (58.1)	204 (55.9)	82 (64.7)	
Indeterminate	58 (11.7)	47 (12.9)	11 (8.7)	
Predominant polarity (Barcelona definition)				
Depressive	94 (19.1)	73 (20.0)	21 (16.5)	8.15 (0.01**)
Mania/hypomania	230 (46.7)	157 (43.0)	73 (57.5)	
Not determined	168 (34.1)	135 (36.9)	33 (25.9)	
Recurrent/unipolar mania				
≥2 episodes of mania without depression	75 (15.3)	45 (12.3)	30 (23.6)	9.30 (0.002**)
At least one lifetime episode with psychotic symptoms	207 (42.1)	149 (40.8)	57 (44.9)	4.11 (0.06)
Disability ≥40%	97 ()	61 (16.7)	36 (36.2)	8.05 (0.005**)
Treatment				
MS + AP	128 ()	83 (22.7)	45 (35.4)	7.88 (0.005**)
MS + AD	17 ()	14 (3.8)	3 (2.4)	0.61 (0.43)
MS + AD + AP	33 ()	28 (7.7)	5 (3.9)	2.10 (0.14)
MS only	69 ()	49 (13.4)	20 (15.7)	0.16 (0.68)
AP only	9 ()	6 (1.6)	3 (2.4)	9.16 (0.02)
AP + AD	4()	3 (0.8)	1 (0.8)	FE=0.36
MS + AP + BZD	70 ()	44 (12.1)	26 (20.5)	2.13 (0.05)
MS + AD + BZD	43 ()	32 (8.8)	11 (8.7)	3.38 (0.06)
MS + AD + AP + BZD	71 ()	63 (17.3)	8 (6.3)	9.16 (0.002**)
MS + BZD	33 ()	25 (6.8)	8 (6.3)	0.04 (0.83)
AP + BZD	4 (0.5)	4 (1.1)	0	FE=0.63
AP + AD + BZD	4 (0.5)	1 (0.3)	1 (0.8)	FE=0.444
APs				
Olanzapine	155 (31.1)	114 (41.2)	41 (32.2)	0.04 (0.82)
Risperidone	45 (9.1)	27 (7.4)	18 (14.2)	5.20 (0.02*)

Contd...

Supplementary Table 5: Contd...

Clinical variables	Whole sample, Mean (SD)/n (%) (n=492)	BD without comorbid substance dependence, Mean (SD)/frequency (%) (n=365)	BD with comorbid substance dependence, Mean (SD)/frequency (%) (n=127)	t-test/Mann-Whitney U test/Chi-square test (P)
Quetiapine	54 (10.9)	39 (10.7)	15 (11.8)	0.12 (0.72)
Aripiprazole	12 (2.4)	9 (2.5)	3 (2.4)	0.004 (1.00)
Lurasidone	9 (1.8)	6 (1.6)	3 (2.4)	0.27 (0.60)
Haloperidol	17 (3.5)	8 (2.2)	9 (7.1)	6.76 (0.009**)
Chlorpromazine	8 (1.6)	3 (0.8)	5 (3.9)	5.71 (0.04*)
ADs				
Escitalopram	20 (4.1)	16 (4.4)	4 (3.1)	0.36 (0.54)
Sertraline	123 (25.0)	119 (32.6)	4 (3.1)	43.59 (<0.001***)
Fluoxetine	20 (4.1)	15 (4.1)	5 (3.9)	0.007 (0.93)
Paroxetine	3 (0.6)	1 (0.3)	2 (1.6)	FE=0.16
Venlafaxine	4 (0.8)	4 (1.1)	0	FE=0.30
Bupropion	6 (1.2)	4 (1.1)	2 (1.6)	FE=0.48
MSs				
Lithium	184 (37.4)	156 (42.7)	28 (22.0)	9.39 (0.002**)
Valproate	227 (46.1)	166 (45.5)	61 (48.0)	0.24 (0.61)
Carbamazepine	13 (2.6)	5 (1.4)	8 (6.3)	8.89 (0.003**)
Lithium + valproate	41 (8.3)	22 (6.1)	19 (14.9)	9.84 (0.002**)
Lamotrigine	5 (1.0)	5 (1.4)	0	1.75 (0.18)
BZDs				
Clonazepam	68 (13.8)	43 (11.8)	25 (19.7)	4.94 (0.02*)
Diazepam	27 (5.5)	9 (2.5)	18 (14.2)	24.89 (<0.001***)
Lorazepam	28 (5.7)	21 (5.8)	7 (5.5)	0.01 (0.91)
Chlordiazepoxide	101 (20.5)	98 (26.8)	3 (2.4)	34.62 (<0.001***)
Etizolam	3 (0.6)	2 (0.5)	1 (0.8)	FE=0.59

AD=antidepressant, AP=antipsychotics, BD=bipolar disorder, BZD=benzodiazepines, FMS=mood stabilizer, SD=standard deviation, # Defined as Body Mass Index > 25 Kilogram/meter²; COBRA: Cognitive Complaints In Bipolar Disorder Rating Assessment; FE= Fischer Exact Test Value; *P≤0.05; **P≤0.01; ***P≤0.001