

A comparative study of clinical correlates of bipolar mixed state with bipolar manic and bipolar depressed state in a general hospital psychiatry setting

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Abstract

Background: Mixed states pose diagnostic dilemmas and raise the question of their existence as separate diagnostic category. There are few Indian studies on mixed affective disorder particularly with respect to the diagnosis and clinical comparison of patients with mixed state and other subtypes of bipolar disorder.

Aim: To elucidate course and clinical correlates in patients with bipolar mixed state and compare them to patients with bipolar depression and mania.

Methods: A total of 70 inpatients of psychiatric ward meeting the inclusion criteria were followed up from the day of admission till discharge and assessed on Hamilton Depression Rating Scale (HDRS), Young's Mania Rating Scale (YMRS), Positive and Negative Symptom scale for Schizophrenia (PANSS), Beck Scale for Suicidal Ideation, Clinical Global Impression Schedule (CGI) and Presumptive Stress Life Event Scale.

Results: Our study found mixed group to be characterized by female preponderance, higher suicidal intent, expression being the first episode, severe illness as rated on CGI-S, increased frequency of psychotic symptoms and mean number of manic and depressive symptoms midway between the other two groups.

Conclusion: The mixed affective state although has clinical correlates that differ from bipolar mania and depression, behaves as interforms of mania and depression.

Keyword: Bipolar mania, Bipolar mixed state, Bipolar depression, Course variables, Clinical profile

Introduction

Mania and Depression are seen as polar opposites. However, since Emil Kraepelin (1904) first described mixed states of manic depressive insanity, it has been known that some patients with acute mania or hypomania simultaneously experience prominent depressive symptoms. According to Kraepelin, the diagnosis of mixed episodes was justified if any elements from affective, psychomotor and cognitive domains were incongruent with the other two and he divided mixed states into six types¹. Although this entity has been identified many years ago, still there is confusion in diagnosing this condition as there is fewer consensuses on the operational diagnostic criteria and inadequate understanding of the evolution of the mixed state.

Studies have shown that incidence of mixed state in bipolar population is high to the range of 31%². Mixed mania was found to be more common in women³. A study by Dell'Osso et al³ found depressive disorders to be common in families of patients with mixed mania. Mixed affective states appeared to be frequently accompanied by psychotic symptoms (often mood incongruent or depressive)³. Dilsaver et al⁴ found that 54.5% with mixed episode were suicidal compared with 2% of patients with pure mania. It was noted by Keller et al⁵ that patients with mixed state have a higher frequency of recurrence and a greater tendency towards

chronicity than individuals with pure mania. Higher rates of co morbid substance abuse, neuropsychiatric abnormalities and obsessive compulsive disorder were found as co morbid conditions with mixed mania³. In view of its specific symptom profile, an attempt to delineate the mixed group based on the clinical characteristics was undertaken and compared with bipolar depressed and manic state.

Aim of the Study

1. To elucidate clinical correlates (family history, suicidal risk, depressive, manic and psychotic symptom severity, comorbidity) in patients with bipolar mixed state and compare them to patients with bipolar affective disorder currently depressed and manic state diagnosed according to ICD-10 DCR.
2. To compare the severity of mania and depression between the three groups (bipolar manic, depressed and mixed state) and analyze the preponderance of specific manic and depressive symptoms within each group.

Subjects and Methods

Study design: Open, Non-Randomized, Naturalistic study with sequential sampling

Study center: Kasturba Hospital, Manipal

Study population: Inpatients of the psychiatry ward, Kasturba hospital, Manipal

Study period: 10 months

Inclusion Criteria: Inpatients of the psychiatry ward, Kasturba hospital, Manipal who are diagnosed to have bipolar affective disorder, current episode being mania, depression or mixed (according to ICD-10 Diagnostic Criteria for Research) by the consultant in charge. They were sequentially selected with no randomization. If a patient has organicity, then the subsequent patient is taken up for the study. Similarly patients who are acutely agitated and violent were taken up for assessments once they settle down.

Exclusion Criteria:

- Non consenting patients
- Patients with diagnosis of schizoaffective disorder or other schizophrenic spectrum disorders
- Patients with neurological disorders or organic brain syndrome.

Subjects meeting the inclusion criteria were taken up for the study after obtaining informed consent. Life chart of the patients were used to collect information on the past episodes. Detailed clinical interview was done by the investigator and the diagnosis was made according to ICD-10 Diagnostic Criteria for Research (ICD-10 DCR). The subjects were assessed at baseline (depending on the patient's cooperation) and 1 week after baseline on the following scales: Hamilton Depression Rating Scale (HDRS), Young's Mania Rating Scale (YMRS), Positive and Negative Symptom scale for Schizophrenia (PANSS), Clinical Global Impression Schedule (CGI), Beck's Scale for Suicidal ideation and Presumptive Stressful Life Events Scale (PSLES). The management plan as decided by the treating psychiatrist was continued. No information regarding the clinical ratings of the patients were suggested to the treating consultant or no change in medications were made based on the rating by the investigator.

ICD-10 DCR Criteria for Bipolar Affective Disorder, Current Episode Mixed

- a. The current episode is characterized by either a mixture or a rapid alternation (i.e. within a few hours) of hypomanic, manic and depressive symptoms.
- b. Both manic and depressive symptoms must be prominent most of the time during a period of at least two weeks
- c. There has been at least one well authenticated hypomanic or manic (F 30.-), depressive (F 32.-) or mixed affective episode (F 38.00) in the past.

Results

A total of 87 patients met the inclusion criteria for the study. After excluding nine persons with inadequate data including two absconders, three persons with physical complications which interfered with

psychiatric management and five other persons whose course could not be followed up in the hospital, a total of 70 patients formed the final sample. Of these 17 patients, 11 were from the bipolar manic group, 1 from the bipolar mixed group and 5 from the bipolar depressed group.

Of the 70 persons included in the study with ICD-10 DCR diagnosis of bipolar manic/bipolar depressed/bipolar mixed state, there was a preponderance of manic group (n1=47), with depressed group being (n2=17) and only 6 (n3) persons with mixed state. For purpose of comparison, manic group will include bipolar disorder currently mania with and without psychotic symptoms and depressive group will include bipolar disorder currently mild, moderate and severe depression with or without psychotic symptoms.

As observed in **Table 1** which shows the socio-demographic profile of patients, the three groups differed in their gender distribution with female preponderance in bipolar mixed group. The mean age at admission during the current episode was 32 years for bipolar mixed group. Almost 67% of those in the bipolar mixed group were married and had completed high school education. Most of our patient population were from low and middle socioeconomic status group.

Table 2 compares the clinical correlates across the three groups. The three groups differed significantly in the presence of psychotic symptoms during the current episode (p 0.005), the bipolar mixed group having the highest proportion and the presence of suicidal ideation (p 0.000), the bipolar mixed group having the highest proportion. However, the groups did not differ significantly on other variables such as substance dependence and presence of stressors. Presence of family history of mental illness shows significance (0.039) with the highest proportion being in the bipolar mixed group.

PANSS rating (**Table 3**) in the present study shows significant differences between groups on Delusions (p 0.02) and Excitement (p 0.005) (almost equal proportions in manic and mixed, less in depressive). Suspiciousness/Persecution (p 0.007) was higher in mixed group compared to manic and depressives.

The mean number of YMRS and HDRS symptoms present in the three groups and their severity scores (**Table 4**) shows highly significant differences. Both symptom and severity scores on YMRS was highest in the bipolar manic group, mid range in the bipolar mixed group and lowest in the bipolar depressive group. Similarly on HDRS, the symptom and severity scores were high in bipolar depressive group, midrange in bipolar mixed group and lower in bipolar manic group.

Table 5 shows distribution of presence of individual manic symptoms on YMRS. In all the symptoms, there is a significant difference between the three groups. On elevated mood, increased motor activity, sleep, irritability, speech, language thought

disorder, content and loss of insight, the depressive group scores less than other two groups.

Table 1: Socio-demographic data of bipolar manic, bipolar depressive and bipolar mixed groups

Socio Demographic Variables	Total Sample (N=70)	Bipolar Manic Group (n 1 = 47)	Bipolar Depressive Group (n 2 = 17)	Bipolar Mixed group (n 3 = 6)
Mean Age (in years +/- SD)	35.81+/-11.69	34.07+/-12.22	41.19+/-13.49	32.17+/-9.36
Gender				
Male	40(57%)	30(64%)	9(53%)	1(17%)
Female	30(43%)	17(36%)	8(47%)	5(83%)
Marital Status				
Married	37(53%)	21(45%)	12(70%)	4(67%)
Single (Unmarried, widow, separated)	33(47%)	26(55%)	5(30%)	2(33%)
Education				
No formal schooling	5 (7%)	3 (7%)	2 (12%)	0
Primary	20 (29%)	15 (32%)	3 (18%)	2 (33%)
High school	39 (56%)	25 (53%)	10 (58%)	4 (67%)
Higher secondary and above	6 (8%)	4 (8%)	2 (12%)	0

Table 2: Clinical Correlates of bipolar manic, bipolar depressive and bipolar mixed groups

Clinical Variables	Bipolar Manic Group N (%)	Bipolar Depressive Group N (%)	Bipolar Mixed Group N (%)	Chi-Square ^a	Sig.
Psychotic symptoms for the current episode	27(57%)	3(18%)	5(83%)	10.67	0.005**
Subjects with presence of stressors in the past one year	37(79%)	14(82%)	4(67%)	0.641	0.726
Number of stressors present (N & %)					
1	25(53%)	7(41%)	3(50%)	2.266	0.687
2	12(25%)	7(41%)	1(17%)		
Presence of suicide ideation during the current episode	9(19%)	8(47%)	6(100%)	17.56	0.001***
Co morbid Substance dependence	3(6%)	1(6%)	0(0%)	0.398	0.820
Family history of mental illness (N & %)					
Present	37(79%)	8(47%)	5(83%)	6.49	0.039*
Major depression	4(9%)	2(12%)	1(17%)		
Bipolar disorder	18(38%)	1(6%)	3(50%)		
Others	15(32%)	5(29%)	1(17%)		
Absent	10(21%)	9(53%)	1(17%)		

a - Kruskal wallis test (df 2) p<0.05* significant; p<0.01 ** very significant p<0.001 *** highly significant

Table 3: Frequency distribution of psychotic symptoms in Study groups

Variables	Bipolar Manic Group N (%)	Bipolar Depressive Group N (%)	Bipolar Mixed Group N (%)	Chi-square ^a	Sig.
Delusions	27(57.4%)	3(17.6%)	4(66.7%)	7.69	0.02*
Conceptual disorganization	9(19.1%)	0(0%)	0(0%)	4.98	0.08
Hallucinatory behavior	9(19.1%)	3(17.6%)	1(16.7%)	0.03	0.98
Excitement	24(51.1%)	1(5.9%)	3(50%)	10.73	0.005**
Grandiosity	28(59.6%)	2(11.8%)	1(16.7%)	13.40	0.001***
Suspiciousness/Persecution	7(14.9%)	2(11.8%)	4(66.7%)	9.97	0.007**
Hostility	12(25.5%)	0(0%)	2(33.3%)	5.73	0.057

a - Kruskal Wallis test (df 2) p<0.05* significant p<0.01** very significant p<0.001 *** highly significant

Table 4: Comparison of Episode Symptoms Severity in Study groups using ANOVA

Symptoms/Severity Mean & S.D.	Bipolar Manic Group	Bipolar Depressive Group	Bipolar Mixed Group	F ^a	Sig.
Total number of manic Symptoms	6.19+/-1.59	0.41+/-0.71	3.67+/-1.63	102.00	0.001***
Total number of depressive symptoms	1.89+/-1.25	6.82+/-1.91	4.83+/-1.32	76.21	0.001 ***
YMRS score	24.14+/-5.39	1.52+/-1.77	14.50+/-3.93	147.65	0.001***
HAMD score	4.42+/-2.90	17.52+/-3.98	13.16+/-4.16	105.55	0.001 ***

a- comparison of means by ANOVA (df2) p<0.05* significant p<0.01 ** very significant p<0.001 *** highly significant

Table 5: Frequency distribution of individual manic symptoms (rated on YMRS) between study groups

Manic Symptoms	Bipolar Manic Group N (%)	Bipolar Depressive Group N (%)	Bipolar Mixed Group N (%)	Chi-square ^a	Sig.
Elevated mood	40(85.1%)	0(0%)	3(50%)	38.21	0.001***
Increased motor activity-energy	39(83%)	2(11.8%)	2(33.3%)	30.76	0.001 ***
Sexual interest	12(25.5%)	0(0%)	0(0%)	7.70	0.021 *
Sleep	35(74.5%)	1(5.9%)	3(50%)	23.54	0.001 ***
Irritability	34(72.3%)	2(11.8%)	6(100%)	23.02	0.001 ***
Speech	35(74.5%)	2(11.8%)	2(33.3%)	20.98	0.001***
Language thought disorder	22(46.8%)	0(0%)	2(33.3%)	13.71	0.001 ***
Content	32(68.1%)	0(0%)	3(50%)	26.16	0.001 ***
Disruptive aggressive behavior	25(53.2%)	0(0%)	1(16.7%)	23.77	0.001 ***
Appearance	18(38%)	0(0%)	2(33%)	8.91	0.012*
Insight	40(85%)	0(0%)	6(100%)	42.80	0.001 ***

a - Kruskal wallis test (df 2) p<0.05* significant p<0.01 ** very significant p<0.001*** highly significant

Table 6: Frequency distribution of presence of depressive symptoms (rated on HDRS) between study groups

Depressive Symptoms	Bipolar Manic Group N (%)	Bipolar Depressive Group N (%)	Bipolar Mixed Group N (%)	Chi-square ^a	Sig.
Depression	5(10.6%)	17(100%)	4(66.7%)	44.50	0.001***
Guilt	0(0%)	8(47.1%)	2(33.3%)	24.17	0.001 ***
Suicide	11(23.4%)	7(41.2%)	6(100%)	14.12	0.001***
Initial insomnia	2(4.3%)	10(58.8%)	0(0%)	27.13	0.001***
Middle insomnia	8(17%)	2(11.8%)	1(16%)	0.26	0.878
Terminal insomnia	0(0%)	12(70.6%)	1(16%)	40.56	0.001***
Work and interests	0(0%)	12(70.6%)	3(50%)	39.55	0.001***
Retardation	0(0%)	7(41.2%)	0(0%)	23.90	0.001 ***
Agitation	17(36.2%)	5(29.4%)	3(50%)	0.82	0.664
Anxiety psychic	23(48.9%)	9(52.9%)	6(100%)	5.52	0.063
Anxiety somatic	7(14.9%)	6(35.3%)	1(16.7%)	3.24	0.197
GI symptoms	3(6.4%)	0(0%)	1(16.7%)	2.37	0.306
General somatic symptoms	9(19.1%)	12(70.6%)	1(16.7%)	15.76	0.001***
Loss of libido	3(6.4%)	3(17.6%)	0(0%)	2.59	0.273
Hypochondriasis	0(0%)	2(11.8%)	0(0%)	6.32	0.042*
Loss of weight	1(2.1%)	6(35.3%)	0(0%)	15.46	0.001***
Loss of insight	40(100%)	0(0%)	6(100%)	1.72	0.422

a - Kruskal wallis test (df 2). p<0.05* significant p<0.01 ** very significant p<0.001 *** highly significant

On sexual interest, disruptive behavior and appearance, the bipolar manic group scores high compared to both depressive and mixed group.

Table 6 shows distribution of presence of individual depressive symptoms on HDRS in the 3 groups. Significant differences are found as follows: On initial insomnia, terminal insomnia, retardation, general somatic symptoms and hypochondrias is, the bipolar depressive group scores high and both manic and mixed groups score low. Whereas, in the items of depression, guilt, suicide and work and interest, both depressive and mixed groups score high as compared to manic group. The other items do not show significant differences.

Discussion

The present study is an attempt to delineate the socio-demographic and clinical profile of naturalistically diagnosed bipolar mixed episodes in comparison with bipolar manic and bipolar depressive episodes using ICD-10 DCR criteria. The idea behind the study was to see whether (as noted by Kraepelin¹, Goodwin et al⁶, Winokur et al⁷, Swann et al⁸) our sample can replicate a unique clinical profile for patients with bipolar mixed state.

In this study, in patients diagnosed by psychiatric consultant as per ICD-10 DCR criteria as bipolar disorder (mania/depression/mixed) were included serially. Since different patients had different periods of stay in the hospital, the rating on HDRS, YMRS and PANSS was done at baseline and the symptomatology was not tracked throughout the stay. The instruments used in the study have been standardized and validated elsewhere and the investigator obtained training to use these scales in his parent department before applying them to the study population. Hence data collected is probably of adequate reliability.

A total of 70 patients formed the final sample of the study. Out of them, there was a preponderance of bipolar manic group (n1=47), followed by bipolar depressed group (n2=17) and bipolar mixed group (n3=6). The three groups differed in their gender distribution with female preponderance in mixed group as observed by Winokur et al⁷ Murphy et al⁹ and Krishnan et al¹⁰. However the definition for the diagnosis used by these authors is different from that in the present study. Furthermore, the sample in mixed state was very small in this study.

Clinical correlates

The present study also found symptom profile which was unique to mixed states. The groups differed significantly in the presence of psychotic symptoms ($p < 0.005$) during the current episode as noted in earlier studies (Table 2). Mood incongruent psychotic symptoms are reported more commonly with mixed states. However, such a distinction was not attempted in the present study. However, the PANSS rating in the

mixed group reflect a high occurrence of delusion, excitement and suspiciousness/persecution – the profile being close to manic than depressive group in this study (Table 3).

Co morbid substance use as found in mixed states in other studies (Himmelhoch et al²) was not noted in the present study. This may be a reflection of generally higher levels of substance use co morbidity in bipolarity reported in western literature as compared to Indian experience.

Also the presence of significant stressors antecedent to the index affective episode in mixed states as noted by Perugi et al¹¹ was not replicated in this study. This finding was in accordance with the studies by Dell'Osso et al³ and Swann et al⁸, who found no significant differences between patients with mixed and non-mixed mania in the frequency of antecedent stressful life events.

Suicidality has been reported to be higher in mixed episode (Dilsaver et al⁴, Tetsuya et al¹²). The present study found significant differences between the groups in the presence of suicidal ideation for the current episode with all the patients in the mixed group having significant intent. Suicidal assessment as a separate variable using the Scale for suicidal ideation was done in this study (Table 2). Comparable information was not found in the literature. However, a highly significant association between suicidal ideation and the status of DSM-IV mixed mania was found in the study by Tetsuya et al¹² who assessed the suicidality using the AMDP system (Association for Methodology and Documentation in Psychiatry). On family history of mental illness, there were significant differences between the groups (0.039) with bipolar mixed states having family history in 5 out of 6 patients of which 3 had a family history of bipolarity (Table 2).

The mean number of YMRS and HDRS symptoms present in the three groups (Table 4) shows highly significant differences - the mean values of the mixed group being midway between those of the manic and depressive groups. This is similar to the findings reported by Marneros¹³, Keller et al⁵ and Swann et al⁸ who described the mixed group as the mid forms between the extremes of mania and depression. Swann et al¹⁴ proposed the presence of 1 or >1 depressive symptoms in the midst of mania for the diagnosis of dysphoric mania. Similarly McElroy et al^{15,16} proposed a criteria which required the presence of a full manic syndrome as defined by DSM-III R accompanied by at least 3 depressive symptoms. In our study, the mean number of depressive symptoms in manic group is 2 whereas, the mean number of manic symptoms in the depressive group is less than 1, thus creating a possibility of mixed manic group being overrepresented in the sample. Furthermore, the mean number of manic and depressive symptoms in the mixed group is almost equal. Interestingly, the mean severity rating on YMRS and HDRS for the mixed group (Table 4) is midway

that of mania and depression supporting the concept of midforms.

When individual symptoms rated as present or absent for all the patients on YMRS and HDRS are analyzed, the striking feature is that the mixed group have a pattern of symptom in part like the manic group and in part like the depressive group (Table 5 & 6). On YMRS, their profile is like mania in items of presence of elevated mood, increased activity, sleep, irritability, speech, language thought disorder, content, appearance and loss of insight and like depression in the relative lack of rating on sexual interest and disruptive behavior.

On HDRS, there is a relative lack of rating on initial and terminal insomnia, retardation, general somatic symptoms, hypochondriasis and loss of weight (like the manic group) and presence of depression, guilt, suicide and interests scores (like the depressive group). This reveals a picture of admixture of symptoms as of mixed group – at least at a cross section, is like an interform of mania and depression in terms of clinical symptoms as noted by Kraepelin¹, Himmelhoch et al¹⁷, Nunn et al¹⁸, Akiskal et al¹⁹, Bunney et al²⁰.

Limitations

A larger sample size through a larger recruitment period would have helped in including more mixed states for more robust findings. A prospective follow up would throw more light on the stability or otherwise of the remitted course in these patients.

Since this study has been exclusively based on the population in a general hospital psychiatric unit in a university hospital which also serves as a tertiary care centre, it is possible that patient's clinical characteristics may differ substantially from clinic based or mental hospital based set up with similar diagnosis. Hence the information of the study has a limited capacity for generalization.

Finally, examining other existing criteria for mixed states may help in delineating or rejecting them as discrete syndromes or disease types.

Conclusion

The study was able to establish some core features that were specific to mixed states such as female preponderance, high suicidal ideation, high family history of mental disorders and high levels of positive symptoms. It also found that mixed states appeared to be true interforms of mania and depression when their symptoms and severity scores were compared, without skewing of the clinical picture grossly to either mania or depression.

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How to cite this article: Krishnan R, Sharma PSVN. A comparative study of clinical correlates of bipolar mixed state with bipolar manic and bipolar depressed state in a general hospital psychiatry setting. *Telangana Journal of Psychiatry* 2016;2(1):31-37.