

## A study of incidence of bipolar disorder in patients treated for major depression

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### Abstract

**Aim:** Recurrent episodes of depression are common in both unipolar and bipolar disorder, but diagnostic and clinical problem with bipolar mood disorder is that hypomanic episodes usually go unnoticed by caretakers and clinicians. Several studies have indicated that if carefully looked for, 25% of patients with major depressive disorder have history of bipolarity. So we aim to assess the proportion of patients with features of bipolar disorder amongst those primarily diagnosed and treated as major depressive disorder and compare the symptom profile of unipolar depression and bipolar depression.

**Methodology:** One hundred consecutive patients, in tertiary care hospital in Ahmadabad, who were being treated as major depressive disorder according to DSM-4 TR and assessed using scales, HAM-D, GAF, Hypomania Check List-32(HCL) and Mood Disorder Questionnaire (MDQ). Patients who scored higher in HCL and MDQ were assessed in details by MINI.

**Results:** 100 patients of unipolar depression were taken in study, out of which 16 patients were found to have bipolar mood disorder after assessment. Our incidence of bipolar mood disorder in patients treated as unipolar depression is 16%. Patients of bipolar depression had significantly higher number of prior mood episodes, family history of mood disorder and episodes with psychotic features. Conclusion - Bipolarity is confidently diagnosable in a substantial proportion of patients being treated as unipolar major depression. All the patients of unipolar depression must be screened for bipolarity to give them specific treatment with better results and better quality of life.

**Keywords:** Major depressive disorder, Unipolar depression, Bipolar depression.

### Introduction

Major depression is one of the most frequent and one of the most disabling psychiatric illnesses. It occurs in 10 to 15% (as per US figures)<sup>1</sup> and 15.9% (as per Indian figures)<sup>2</sup> of general population during their lifetime. Recurrent episodes of depression are common in both unipolar and bipolar disorder, but diagnostic and clinical problem with bipolar mood disorder is that hypomanic episodes usually go unnoticed by caretakers, and also they just consider it as phase of over activity as it causes less or no distress to patients as well as caretakers. Whereas depressive episodes, which also have frequent occurrence are distressing and patients seek treatment for that. As a result, clinicians usually treat the depressive episodes but tend to miss history of hypomanic episodes and on occasion, full-fledged manic episodes results.<sup>3,4</sup> Several studies<sup>5-10</sup> have indicated that if carefully looked for, 25% of patients with major depressive disorder have history of bipolarity and few study report that figure is as high as about 50%. General population does not perceive hypomania as pathological and busy clinicians do not always make relevant and detailed inquires about past manic or hypomanic episodes of patients presenting with major depressive disorder, so diagnosis of bipolar mood disorder is delayed for<sup>8-10</sup> years according to a number of studies carried out in past.<sup>3,4,11,12</sup>

Manning JS et al<sup>5</sup> conducted a study (1997) in 108 patients of both anxiety and depression. 25.9% patients had bipolar I or II or III disorder or cyclothymia. Bipolar spectrum disorder was more common 33.3% within the depressive group as against anxiety group, amongst which bipolar II disorder was more common. Angst et al<sup>9</sup> made national co morbidity survey replication between February 2001 to April 2003. Nearly 40% of study population with

history of major depressive disorder had history of sub threshold hypomania. Bschor et al<sup>13</sup> conducted a study with similar objectives, it showed that out of total 252 patients being treated as major depressive disorder, 11.6% of patients had undiagnosed bipolar disorder according to DSM IV TR whereas according to bipolarity specifier algorithm (which expands DSM IV criteria) showed 24.8% prevalence of bipolarity was found in the same patient population. Later in 2008 Angst et al<sup>14</sup> conducted multi centric multinational study in a large patient population of 5635 and found that 16% patients with major depressive disorder fulfilled DSM IV criteria for bipolar disorder when interviewed carefully, using very reliable and valid screening instruments. Hu C<sup>15</sup> in a similar study conducted in China in 2012 showed around 20.8% prevalence of bipolarity in patients of being treated as major depression.

Anti-depressants are robustly used psychotropic medications in field of psychiatry as well as general medicine. Effects of anti-depressants in controlling depressive episodes are well established. But anti-depressants don't offer any mood stabilizing properties. Moreover, Anti-depressant medications can adversely affect the long term prognosis by inducing manic switch, more frequent depressive episodes and also treatment refractoriness as statistically shown in study by Sharma et al.<sup>16</sup> Such patients are better treated with a combination of mood stabilizers and antipsychotics than with antidepressants alone.<sup>17</sup>

Ghemi et al<sup>18</sup> reviewed 85 patients with depression. 37% of bipolar depression was misdiagnosed as unipolar depression. Anti-depressants were used earlier and more frequently than mood stabilizer. 23% of patients experienced worsening of course of illness in the form of

causing more frequent episodes after anti-depressant use. Wehr et al<sup>19</sup> and Alfshuler LL et al<sup>20</sup> study results showed similar results implying use of anti-depressants alone in bipolar depression induces more frequent episodes, chronicity and thus increasing disability and overall burden.

There are clear differences in the optimal management of both bipolar and unipolar depression. So it is important to distinguish between these two conditions clinically. It is commonly assumed that there are no important differences between unipolar and bipolar depression clinically. But many a times, patients with bipolar mood disorder have their first episode of illness as depression rather than mania, so it is desirable to recognize and differentiate in order to treat specifically in the early stage of illness.

Liz forty et al<sup>21</sup> (2008) carried out a study in 593 patients of unipolar major depression and 443 patients of bipolar mood disorder and studied clinical presentation of depression amongst them. Depression was associated with presence of psychotic features, diurnal variation of mood, and hypersomnia during depressive episodes and greater number of episodes. Benazzi et al<sup>6</sup> (1997) made a cross sectional epidemiological survey of 203 consecutive patients of major depression in a private setting. They found that patients of bipolar disorder II were associated with early age of onset and more atypical features, psychotic features and more frequent depressive episodes.

In an Indian study of 2017 by Kamal et al,<sup>22</sup> which compared socio demographical correlates of unipolar and bipolar depression, in study 330 cases were taken out of which 164 of unipolar depression and 166 of bipolar depression. They found male gender, employment status, Hindu religion, onset of illness and chronicity are risk factors for bipolar depression. A similar study by Nisha et al<sup>23</sup> 2015, found that bipolar depression had younger age of onset, longer duration of illness, more frequent episodes and hospitalization. Psychotic symptoms like delusion and auditory hallucination were significantly high in bipolar depression patients. The new diagnostic category in DSM 5 untitled Major Depressive Disorder with mixed features is applied to individuals who meet criteria for MDD and have concurrent sub syndromal hypomanic or manic features. Mixed symptoms are more common in bipolar depression than unipolar depression. Research over several years made it clear that careful differentiation of unipolar depression and undiagnosed bipolar illness and its specific treatment helps in reducing the morbidity associated with it.

### Aims and Objectives

1. To study incidence of bipolar disorder in diagnosed cases of major depressive disorder.
2. To compare the symptom profile of unipolar depression and bipolar depression.

### Methodology

Source and Collection: One hundred consecutive, outdoor and indoor patients from Department of Psychiatry, tertiary care hospital in Ahmadabad, who were being treated as Major Depressive Disorder according to DSM-4 TR and

were receiving antidepressant medications, were included in the study. A convenience sampling technique was used and institutional ethical committee approval was taken. All the patients were above age of 18 years and have informant available. Participants were included in the study after taking informed consent.

### Exclusion criteria

1. Those who were unwilling for the interview
2. Those who had medical emergencies.
3. Those who had co morbid psychiatric illnesses like substance use disorder, personality disorder or obsessive compulsive disorder, mental retardation, seizure disorder, cognitive impairment, permanent neurological deficit, affective illness secondary to substance use, psychosis outside mood episode.

Procedure and Assessment: Each participant completed a case sheet with demographic information, current clinical diagnosis, treatment received and previous psychiatric consultation or hospitalization if any, to establish a diagnosis of depression and to check severity of episodes following scales were applied.

### Scales

#### Hamilton rating scale for depression (HAM-D)<sup>24</sup>

The 21-item HAM-D for assessing the severity of depression was developed by Max Hamilton in 1960. It is instrument for rating depression with very high reliability and validity. It is a time tested instrument. Each item is scored from 0-4 or 0-3 or 0-2 with score range of 0- 66. Higher the score, higher the severity of depression.

#### GAF (Global Assessment of Functioning)<sup>25</sup>

Scale was developed by Jones et al with reasonable reliability and validity. Impairment in psychosocial and occupational functioning as well as personal care and symptoms severity is taken into consideration. It does not include impairment due to physical or environmental conditions. The score ranges from 0 to 100. It has been objectively specified that loss of progressive functioning reduces the total score. Lower the score, poorer the global functioning of patient.

#### Hypomania Check List -32:<sup>26</sup>

This scale was developed by J. Angst, R. Adolfsson and colleagues in 2004-05 with sensitivity of the instrument 80% and specificity of 51%. It is a self-reported instrument which consists of 32 statements. The patient has to answer yes or no. Each yes is given a score of 1 and the total gives the final score. An HCL score range from 0-32, the cut off is 14 for positive result.

#### Mood Disorder Questionnaire (MDQ):<sup>27</sup>

It was developed by Hirschfield et al (2000). It has sensitivity of 0.73 and specificity of 0.90. It is also a self-reported instrument. It basically pertains to hypomania symptoms. It consists of 13 questions. The patient has to answer yes or no. Each yes is given a score of 1 and the total

score is final score. Range is 0-13 and cut off for positive result is 7. There is also specifier that those symptoms occurred during same period. Subjective distress ranging from no distress to severe distress is also noted.

HCL 32 and MDQ Gujarati versions were used. The cronbach alpha for the translation was 0.959 and 0.943 which indicate very good reliability. The educated patients completed these on their own, while those who had no formal education, data were completed by verbally reading out by the researcher.

Patients who scored 14 or more on HCL32 and /or score 7 or more on MDQ were assessed in detailed by MINI (International Neuropsychiatric Interview) (Sheehan et al.1998)<sup>26</sup> for the presence of Axis I disorders according to DSMIV The patients were categorized into 2 main subgroups (Bipolar disorder, Bipolar –I and Bipolar–II vs. No bipolar Disorder).

**Analysis**

Demographic characteristics and disorder related characteristics were tabulated. On the MINI interview, Patient who were found to have Bipolar Disorder and those who had no Bipolar disorder were compared regarding demographic characteristics, disease related characteristics (duration, number of episodes, age at onset, family history, past history of suicide attempt, psychotic feature, diurnal variation) and Global assessment of functioning. The groups were compared using chi square, t test, Yates correction and mid-p (as appropriate). P<0.05 was considered statistically significant. SPSS version 17 was used to analyze the data.

**Results**

**Table 1:** Demographic characteristics

		Number of Patients n=100
Sex	Male	35
	Female	65
Marital status	Single	7
	Married	79
	Widowed	13
	Divorced	1
Occupation	Professional	3
	Clerical	1
	Skilled work	4
	Semiskilled work	26
	Unskilled work	27
Education	Unemployed	39
	Graduate	5
	Post high school	6
	High school (matriculation)	18
	Middle school	25
Income	Primary school	27
	Illiterate	19
	9798-19574	5
	7323-9797	9

	4891-7322	25
	2936-4890	27
	980-2935	13
	Up to 980	21
Religion	Hindu	79
	Islam	17
	Sikh	3
	Others	1
Family type	Nuclear	51
	Joint	49
Locality	Urban	85
	Rural	15

100 patients, diagnosed and treated as Major Depressive Disorder were taken into study. Demographic characteristic analysis of total sample shows mean age of 39.8 years, majority of selected patients were married females (around 52%). 61% of the patients visiting our centre come from lower socio economic class and are not well educated. (89% were below or at matriculation level). 85% patients had no history of suicide and there was no family history of any psychiatric illness in 80%.

**Table 2:** Disease related characteristics

		Number of Patients N=100
Suicide	0	85
	1	5
	2	5
	3	3
	4	2
Diurnal variation	No	51
	Worse in am	21
	Worse in pm	28
Psychotic features	No	76
	Suspicious	16
	Ideas	5
	Delusions	3
Family history	Positive	20
	Negative	80
	MDD	5
	BMD	6
	Psychosis	5
GAF	Others	4
	41-50	7
	51-60	31
	61-70	44
	71-80	16
	81-90	2

**Table 3:** Comparison of patients having Unipolar Depression (MDD) and Bipolar Mood Disorder (BMD)

		Unipolar depression		Bipolar depression		
		Number/ mean	Percentage/sd	Number/ mean	Percentage/sd	
Age		42.54	11.69	37.25	10.73	t – 3.5841 p = 0.0105
Sex	Male Female	30 54	35.7 64.3	5 11	31.3 68.8	Chi square=0.116 p=0.36
Marital status	Single Married Widowed Divorced	5 65 13 1	6 77.4 15.5 1.2	2 14 0 0	12.5 87.6 0 0	Chi square=3.664 p=0.16.1
Occupation	Professional Clerical Skilled work Semiskilled Work Unskilled Work Unemployed	2 1 4 21 23 33	2.4 1.2 4.8 25.6 27.4 39.3	1 0 0 5 4 6	6.3 0 0 31.3 25 37.6	Chi square=0.122 p= 0.9409
Education	Post Graduate High High school Middle school Primary school Illiterate	4 4 13 22 23 18	4.8 4.8 15.5 26.2 27.4 21.4	1 2 5 3 4 1	6.3 12.5 31.3 18.8 25 6.3	Chi square=4.737 p= 0.1889
Income Kuppuswamy classification	9798-19574 7323-9797 4891-7322 2936-4890 980-2935 UP TO 980	3 8 20 25 12 16	3.6 9.5 23.8 29.8 14.3 19.0	2 1 5 2 1 5	12.5 3.6 31.3 12.5 6.3 31.3	Chi square=0.6249 p=0.73
Religion	Hindu Islam Sikh Others	64 16 3 1	76.2 19 3.6 1.2	15 1 0 0	93.8 6.3 0 0	Chi square=2.581 p=0.2751
Family type	Nuclear Joint	44 40	52.4 47.6	7 9	43.8 56.3	Chi square=0.4 p=0.2638
GAF	41-50 51-60 61-70 71-80 81-90	7 26 37 12 2	8.33 30.95 44.04 14.28 2.38	0 5 7 4 0	0 31.25 43.75 25 0	Chi square=0.74 p=0.688

On HCL 32, score 14 or more was obtained by 19 patients. That indicates positive bipolarity in 19 patients Using MDQ, 18 patients showed score of 7 or more which again is indicative of bipolarity. All these 19 patients, who were screened positive for bipolar mood disorder, were subjected to MINI to confirm the diagnosis. Out of 19, 16 patients fulfilled the criteria for bipolar mood disorder out of which 9 had bipolar mood disorder type II (with current or past hypomanic episode) and 7 had bipolar mood disorder type I (with current or past manic episode) So out of 100 patients being treated as unipolar depression, 16 patients had bipolar mood disorder.

**Table 4:** Comparison of disease related characteristics

		Unipolar Depression (n=84)	Bipolar Disorder (n=16)	
Duration	Range	3-420	1-288	t= 0.4151
(in months)	Mean	78.61	88.31	p=0.6790
	SD	88.29	87.79	
	Median	48	48	
Number of	Range	1-15	1-24	t=4.4672

Episodes	Mean	3.5	8.15	p=0.0001
	SD	2.95	6.78	
	Median	2	6	
Family History of any	Present	15	5	Chi square=0.789
	Absent	69	11	p= 0.1877
Psychiatric Illness				
Family History of Mood Disorder (Bipolar Disorder or Depression)	Present	7	4	Chi square=2.301
	Absent	77	12	p= 0.043

In our study, out of 100 patients treated for depression, after assessment we found that 16 patients diagnosed having bipolar mood disorder and 84 diagnosed with unipolar depression. Patients having Bipolar Mood disorder were significantly younger than unipolar depression. No significant difference was found in sex, marital status, education, religion, income, family type, occupation or locality between two groups. Number episodes of illness were significantly higher in bipolar mood disorder than unipolar. Family history of mood disorder was significantly higher in bipolar disorder group than unipolar.

Using age of the patient and duration, after mathematical calculations, it showed mean age of onset for unipolar depression is 35.59 years as compared to bipolar depression for which mean age of onset is 29.9 years. The two tailed P value equals 0.1072. Although the difference does not reach statistically significant level, but apparently bipolar depression has early age of onset compared to unipolar depression patients.

**Table 5:** Comparison of clinical features

		Unipolar Depression (n=84)	Bipolar Disorder (n=16)	
H/O Suicide attempt	Present	11	4	Chi square=0.70 p=0.2005
	Absent	73	12	
Diurnal variation	Present	44	5	Chi square=2.40 p=0.06
	Absent	40	11	
Psychotic features	Present	17	7	Chi square=7.66 p=0.021
	Absent	67	9	

In clinical features, there was no significant difference in suicide attempt between both groups. Significant difference was found in diurnal variation as 55.5% patients of unipolar depression shown symptoms diurnal variation where only 18% patients of Bipolar depression shown that symptoms. Psychotic features were significantly higher in bipolar mood disorder patients than unipolar depression.

## Discussion

### Incidence of undiagnosed bipolarity

Our incidence of bipolar mood disorder in patients treated as unipolar depression is 16% which is similar to that found in much larger multicentre studies in various parts of the world including UK, Asian countries like China. Angst et al<sup>14</sup> had prevalence of 16%, Hu c et al<sup>15</sup> 20.8%, Smith et al<sup>29</sup> 3.3 to 21% of undiagnosed bipolarity. It goes on to confirm that in a substantial chunk of patients being treated as major depression, bipolarity would go undiagnosed and untreated in absence of high index of awareness. Therefore these

patients would be bereft of the advantage of more specific and more efficacious treatment of bipolar mood disorder as against the treatment of unipolar depression only.

### Age of onset

Our study showed apparent difference in age of onset where bipolar depression group showed younger age of onset with mean age of onset being 29.9 years as compared to unipolar for which it is 35.5 years. BRIDGE<sup>13</sup> study showed younger age of onset of psychiatric symptoms before 30 years of age in bipolar depression compared to unipolar depression. Smith et al<sup>29</sup> showed similar results. Study showed mean age of onset 20 years for bipolar depression and 26.6 years for unipolar depression. Those were in keeping with our study. A study by Nisha et al<sup>23</sup> also showed early age of onset in bipolar depression than unipolar depression. It suggests that clinicians should take extra precaution and screen for bipolarity features before using antidepressants

alone when patient presents with depression in early life especially adolescents and young adults.

### Prior mood episodes

In our study, results showed that patients with bipolar depression were associated with more frequent mood episodes (mean: 8.125) as compared to those with unipolar depression (mean: 3.5). According to Smith et al,<sup>29</sup> bipolar mood disorder group demonstrated average 6 episode as compared to depression group who showed 3 episodes as an average. Whereas Angst et al<sup>14</sup> study results shows that history of prior mood episodes (2 or more) was present in bipolar depression and statistically significant difference was there amongst unipolar and bipolar depression. In a study by Nisha et al<sup>23</sup> shown similar results as bipolar group had more frequent episodes than unipolar. This indicates bipolarity has a more chronic course with multiple mood episodes ultimately resulting in poorer prognosis in the long run. Therefore it is all the more important to detect it with high index of suspicion and give the patient better quality of life with specific treatment.

### Family history of mood disorder

Our study showed statistically significant higher chances of positive family history for mood disorder for bipolar depression than in those with unipolar depression ( $p < 0.043$ ) that bipolar depression had higher rates compared to unipolar depression. Family history of mania was significantly positive in bipolar mood disorder as compared to unipolar in BRIDGE study,<sup>13</sup> whereas in Smith et al<sup>29</sup> it showed no significant difference for family history of mood disorder in both bipolar and unipolar depression group. Judith et al<sup>30</sup> conducted study in 74 subjects with depressive episodes (including both unipolar and bipolar mood disorder) from NIMH clinical research centre of study of depression in Duke University. Study suggests bipolar patients have higher rate of positive family history of mood disorder as compared to unipolar depression patients. Mitchell et al' 2001<sup>31</sup> found similar results when study done in 270 patients of unipolar and bipolar depression. This suggests that positive family history in bipolar mood disorder is bad prognostic indicator in long run hence, it is important to diagnose or rule out carefully.

### Psychotic features

Our study results show significant difference between unipolar and bipolar depression as far as psychotic features are concerned ( $p < 0.021$ ), the incidence being higher in patients of bipolar depression. Goes FS et al<sup>32</sup> conducted a cross sectional study 4724 subjects of major depression and bipolar mood disorder and found that psychotic features during depressive episode increases likelihood of diagnosis of bipolar mood disorder. ( $p < 0.0005$ ) Angst et al<sup>14</sup> study results also states the likelihood of bipolarity if episode of depression is associated with psychotic features. Nisha et al<sup>[23]</sup> found similar results as psychotic symptoms like delusion, auditory hallucination and Schneider's first rank symptoms were significantly high in bipolar group. As these

studies suggest more association of psychotic features with bipolar depression, it might require anti-psychotic drugs with all the resultant implications.

### Common Clinical manifestation of Mania and Hypomania

Results shows that both HCL 32 and MDQ in patients of bipolar depression, most common features are related to irritability, increased self-confidence and talkativeness. These results are consistent with review done by RAO GP<sup>33</sup> on Indian research on bipolar disorder, according to which irritability was 82%, aggression was 70%, and euphoria was 50% in patient sample.

### Global assessment of functioning

In our study, we found no statistically significant difference between the global assessment of functioning in unipolar and bipolar depression. These findings is similar to the findings of Dorz S et al<sup>34</sup> (2003) study conducted in 162 inpatients of depression. Whereas our findings are contrary to those of Smith et al,<sup>29</sup> Angst et al<sup>14</sup> conducted study in 576 and 5635 patients respectively which were multi centric cross sectional study. The difference in the studies can probably be explained by the fact that our study and similar study was conducted a smaller patient sample respectively, whereas the two studies showing positive correlation of higher functional impairment and bipolarity were conducted on a much larger patient sample of 576 and 5635. Hence, it may be inferred that our study needs replication on much larger scale before conclusion can be made regarding this research impact.

### Conclusion

It is clear that with high index of suspicion, bipolarity is patently diagnosable in a substantial proportion of patients being treated as unipolar major depression. They have difference in clinical features from unipolar depression in the form early age of onset, positive family history for mood disorder, more number of mood episodes and presence of psychotic features during the depressive episode and course of illness.

Although conducted on a limited numbers of patients and therefore the need to replicate it in larger study groups, the clinical inference of our study is quite clear. All the patients of unipolar depression must be screened for bipolarity to give them specific treatment with better results and better quality of life.

### Limitation

This study being a cross sectional study with some limitation like smaller sample size and confounding factors were not taken into account.

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