A study to identify unrecognized bipolar disorder in patients of major depressive disorder taking antidepressants

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ABSTRACT

Background: Unrecognized bipolar spectrum disorder under cover diagnosis of major depression disorder leads to wrong medications (antidepressants in absence of mood stabilizer), which may switch to mania. **Aims and Objectives:** A study was to identify unrecognized bipolar disorder in patients of major depressive disorder taking antidepressants. **Materials and Methods:** This is an observational and cross-sectional study of 150 patients previously diagnosed as major depressive disorder taking antidepressants from tertiary care hospital. Patients were assessed by proforma containing demographic details, Questionnaire of mood disorder questionnaire (MDQ), and Hamilton depression rating scale (HAMD) followed by clinical interview according to DSM-5 to confirm diagnosis. Statistical analysis was done. **Results:** We found 6.67% depression patients screened positive on MDQ for bipolar disorder and diagnosis is confirmed by interview according to DSM-5. MDQ positive patients have early age of onset of depression($P = 0.0109$), long duration of depression($P = 0.0478$), presence of previous suicide attempt($P = 0.0130$), and family history of bipolar disorder($P = 0.0361$). No statistically significant difference was observed between mean HAMD score and severity of depression between MDQ positive and negative group. **Conclusion:** Among patients prescribed antidepressants for depression, there is a substantial proportion with unrecognized bipolar disorder and most of them had never received diagnosis of bipolar disorder. When seeing patients with depression disorder, clinicians should review the life history for screening of unrecognized bipolar disorder by looking for early age onset of depressive episode and long lifetime duration of depression, previous suicide attempt, and family history of bipolar disorder.

Key words: Unrecognized; Bipolar disorder; Major depressive disorder; Antidepressants

INTRODUCTION

Bipolar disorder can be seen as a spectrum condition[1,2] and represents a continuum of mood changes of different severities ranging between full blown mania and unipolar depression.[3] Bipolar disorder affects about 2% of the population.[4] It is the sixth leading cause of disability worldwide.[5]

Population surveys using structured diagnostic interviews and standardized criteria report lifetime prevalence rates to be 1.0% for bipolar I disorder, 1.1% for bipolar II disorder, and 2.4% for subthreshold bipolar disorders.[4] However, it was demonstrated recently that this prevalence exceeded 5%.[6,7] This variation in prevalence is explained by the long delay of diagnosis of bipolar disorder.[8] Indeed, these patients often had initially a major depressive episode and they were wrongly diagnosed as an unipolar depression in different proportions going from 30% to 50%.[6] The mean delay between first onset of mood symptoms and receiving a correct bipolar diagnosis is estimated around 10 years.[9-11] Thus, delayed diagnosis could increase antidepressant-

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induced manic episodes, occur rapid cycling, resistance due to anti-depressant drugs and a highest risk of suicide[12,13] and also poorer quality of life, greater functional impairment, and increased health-care cost.[14-16]

Identification of past history of hypomania can be difficult, as a majority of patients seek treatment during their depressive rather than hypomanic episodes.[17] Hypomania can be particularly difficult to differentiate from normal mood. The use of clinical predictors and screening instruments can improve the recognition of bipolar disorder[18]

Aims and objectives

The current study was conducted to identify unrecognized bipolar disorder in patients of major depressive disorder taking antidepressants.

MATERIALS AND METHODS

This is a cross-sectional and observational study, conducted from May 2018 to April 2019 among outdoor patients of the psychiatry department of a tertiary care multi-specialty hospital.

Prior approval from the Local Ethics Committee (Institutional Review Board) was taken. One hundred and fifty outdoor patients evaluated at department of psychiatry, previously detected with major depressive disorder according to DSM-5 criteria, and currently on anti-depressant treatment was taken up in the study. They were then screened for inclusion and exclusion criteria. Written informed consent from every participant was taken after explaining the purpose of the study. Anonymity and confidentiality of participants were maintained. Interview was taken in participant's vernacular language (Gujarati) or Hindi or English.

Every patient's responses were recorded in a proforma containing details of demographic variables such as participant's initials, age, gender, religion, residence, occupation, gross family income, marital status, education, stressor before start of illness, previous attempt of suicide, and family history of psychiatric illnesses were included in the proforma. The mood disorder questionnaire (MDQ) and Hamilton depression rating scale (HAM-D) were applied on patients followed by clinical interview according to DSM-5 criteria to confirm diagnosis.

Scales used

The MDQ
The MDQ is a self-report screening inventory for Bipolar Spectrum Disorder (which includes Bipolar I, Bipolar II, and Bipolar NOS). The MDQ is a screening instrument and not a diagnostic tool. MDQ having sensitivity of 73% and specificity of 90% in an outpatient psychiatric sample.[19]

The MDQ consists of 15 questions and takes about 5 min to complete. The first 13 questions about possible symptoms are answered either "yes" or "no." Additional questions are about cooccurrence of symptoms during the same period of time (yes/no question) and about the severity of functional impairment caused by the symptoms on a 4-point scale.

Positive Screen: All three of the following criteria must be met:
Question 1: Seven out of 13 positive (yes) responses
Question 2: Positive (yes) response
Question 3: "Moderate" or "Serious" response

The original questionnaires were translated into Gujarati language by committee approach. In the present study, the Cronbach's alpha coefficient for the Gujarati translated version of MDQ was 0.736.

HAM-D
The questionnaire is designed for adults and is used to rate the severity of their depression, containing 21 questionnaire items with score ranging from 0=not present to 4=severe. First, 17 questions are used for rating severity of depression. It has sensitivityof 86.4% and specificity of 92.2%[20] 0–7=no depression, 8–13=mild depression, 14–18=moderate depression, 19–22=Severe depression, and >23=Very severe depression

Statistical analysis was done. Qualitative data variables were expressed by using Frequency and Percentage. Chi-square test/Fisher's exact test was used to find the association between 2 qualitative data variables. Quantitative data variables were expressed using Mean and Standard Deviation. Mann–Whitney test was used to find the significant difference between mean score with in two independent groups. Frequency estimates were determined with 95% confidence intervals. All statistical analyses were two-sided, and a probability level of <0.05 was established as statistically significant.

Inclusion criteria
The following criteria were included in the study:
1. Age >18years
2. Patients who were willing to give informed consent.
3. Patients of major depressive disorder taking antidepressants.(Diagnosed according to DSM 5)

Exclusion criteria
The following criteria were excluded from the study:
1. Patients who were not ready to give informed consent
2. Patients of Major depressive disorder with comorbid psychiatric disorders

3. Patients having substance abuse except tobacco.
4. Known patient of bipolar spectrum disorder, having known history of mania and hypomania
5. Patients stopped taking the antidepressants because antidepressants were not being prescribed for depression or they were not currently suffering from depression.

RESULTS

In this study, recruited patients' age range from 21 to 75 years with mean age is 46.33±11.93 years. Among them, 61% were female and 39% were male. About 6.67% (10 out of 150) patients screened positive on MDQ.

Group comparisons regarding MDQ-positive and negative with various demographic variables are shown in Table 1, among them unemployment, unmarried, presence of previous suicide attempt, duration of depression, and age at onset of depression have statistical significant difference between MDQ-positive and negative group.

MDQ individual component comparison and interpretation are shown in Table 2. It showsthat all 17items of the MDQ were significantly associated with screening positive for bipolar disorder (P<0.001). History of blood relative having bipolar disorder was more common in MDQ-positive patient compared to MDQ-negative patient and statistically significant. No statistical significant difference between mood disorder-positive and negative patient for question asking "health professional ever told you have bipolar disorder" with majority answering "no" in both group. Suggesting need of MDQ like scale for screening of bipolar mood disorder.

Table 1: Comparison of demographic variables and other factors related to depression between MDQ-positive and negative group

Demographic Variables	Total (n=150)	Mood disorder questioners		P value
		Positive (n=10)	Negative (n=140)	
Age (Mean years)	46.33±11.93	40±7.53	46.79±12.08	0.0834*
Gender				
Male	59	5	54	0.5156+
Female	91	5	86	
Religion				
Hindu	126	9	117	1.0000+
Muslim	24	1	23	
Residence				
Rural	32	3	29	0.3761+
Town	41	4	37	
Urban	77	3	74	
Occupation				
Unemployed	73	1	72	0.0362+
Labor	55	5	50	
Semi-Professional	17	3	14	
Professional	5	1	4	
Gross family income (Rupees)				
≤7000	88	3	85	0.0930+
>7000	62	7	55	
Marital status				
Unmarried	6	2	4	0.0261+
Married	118	7	111	
Divorced/Widow/Separated	26	1	25	
Education				
Illiterate	39	2	37	0.8737+
School (primary/secondary)	100	7	93	
College (Graduate/postgraduate)	11	1	10	
Stressor before start of illness				
Yes	108	6	102	0.4672+
No	42	4	38	
Previous suicide attempt				
Yes	36	6	30	0.0130+
No	114	4	110	
Family history of psychiatric illness				
Yes	30	2	28	1.0000+
No	120	8	112	
Depression duration (years)	6.17±5.35	9.0±5.27	5.97±5.32	0.0478*
Age at onset of depression (years)	40.19±12.58	31.00±5.70	40.85±12.69	0.0109*

*Mann–Whitney test, +Fisher's Exact test, +Chi-squared test

Table 2: MDQ individual component comparison and interpretation

QUESTION	Symptom	Total n=150 (100%)	MDQ +ve n=10(%)	MDQ –ve n=140(%)	P value*
a. Felt so good or hyper	Present	6 (4)	5	1	<0.001
	Absent	144 (96)	5	139	
b. Were so irritable	Present	45 (30)	9	36	<0.001
	Absent	105 (70)	1	104	
c. Felt more self-confident	Present	11 (7.33)	7	4	<0.001
	Absent	139 (92.67)	3	136	
d. Got much less sleep	Present	14 (9.33)	9	5	<0.001
	Absent	136 (90.67)	1	135	
e. Were more talkative	Present	26 (17.33)	7	19	0.002
	Absent	124 (82.67)	3	121	
f. Had racing thoughts	Present	31 (20.67)	10	21	<0.001
	Absent	119 (79.33)	0	119	
g. Were so easily distracted	Present	13 (8.67)	7	6	<0.001
	Absent	137 (91.33)	3	134	
h. Had more energy	Present	10 (6.67)	8	2	<0.001
	Absent	140 (93.33)	2	138	
i. Were more active	Present	10 (6.67)	5	5	<0.001
	Absent	140 (93.33)	5	135	
j. Were more social	Present	10 (6.67)	7	3	<0.001
	Absent	140 (93.33)	3	137	
k. Were more interested in sex	Present	5 (3.33)	4	1	<0.001
	Absent	145 (96.67)	6	139	
l. Did unusual things	Present	7 (4.67)	6	1	<0.001
	Absent	143 (95.33)	4	139	
m. Spent more money	Present	5 (3.33)	4	1	<0.001
	Absent	145 (96.67)	6	139	
Concurrent symptoms	Present	19 (12.67)	10	9	<0.001
	Absent	131 (87.33)	0	131	
a. to m. Causing moderate/ serious problem	Yes	11 (7.33)	10	1	<0.001
	No	139 (92.67)	0	139	
Blood relatives having bipolar disorder	Yes	5 (3.33)	2	3	0.0361
	No	145 (96.67)	8	137	
Health professional told you have bipolar disorder	Yes	1 (0.67)	1	0	0.0667
	No	149 (99.33)	9	140	

*Fisher's exact test

No statistically significance difference in severity of depression or means score of Hamilton depression rating scale (HAMD) between MDQ positive and negative patients is shown in Table 3.

DISCUSSION

Our study found 6.67% (10 out of 150) patients of major depressive disorder taking antidepressant screened positive on MDQ which is consistent with some earlier study. Daniel J. Smith, Emily Griffiths et al., study found that between 3.3 and 21.6% of primary care patients with unipolar depression may have an undiagnosed bipolar disorder.[21] A study by Tom Hughes et al., found that the prevalence of unrecognized bipolar disorder was 7.3% among UK primary care patients prescribed antidepressants. Adjusting for differences between the sample and a national database gives a prevalence of 10.0%.[22] Kamat et al., in his study found that 6.9% among patients with major depressive disorder in a commercially insured population screened positive for bipolar disorder on MDQ.[23] Our study

Table 3: Comparing HAM-D score between MDQ-positive and negative group

HAM-D SCORE	MDQ Positive n=10	MDQ Negative n=140	P value
Normal (0–7)	5	83	0.6002*
Mild depression (8–13)	3	32	
Moderate depression (14–18)	1	12	
Severe depression (19–22)	0	8	
Very severe depression(≥23)	1	5	
Mean±SD	10.1±8.95	7.22±6.92	0.2549†

*Chi-Squared Test for Trend, † Mann–Whitney test

found no statistically significant mean age(Mean age in years 40±7.53 in MDQ positive), gender, and education difference between the groups. MDQ-positive subjects were less likely to be married (P=0.0261). MDQ-negative subjects were less likely to be employed in our study, MDQ-positive subjects were more likely from labor and semi-professional group (P=0.0362).

Furthermore, consistent with the previous study by Oneib Bouchra et al., Shabani et a l., and many other, we found

that the previous suicide attempt(P=0.0130) is more likely to present in MDQ positive compare to negative patient.[24-28] Consistent with the previous study by John et al., Benazzi, and many others, family history of bipolar disorder(P=0.0361)[28,29] is more likely to present in MDQ-positive compare to negative patient. We found early age at onset of depression(P=0.0109) and have long duration of depression that is more common(P=0.0478) in MDQ-positive compare to negative patients which is consistent with Oneib Bouchra et al., study[24]. Our study found that out of those screened positive, 90% (9/10) had never received diagnosis of bipolar disorder, which is also interpreted in Robert et al.[30]

In our study over all patients (both MDQ-positive and negative), more common symptoms reported are irritability (30%) followed by racing thoughts (20.67%) and talkativeness (17.33%) whereas increase interest in sex (3.33%) and excessive money spending (3.33%) are reported less on MDQ. In Robert et al., study, endorsement of symptoms in entire sample (n=649) found that easy distractibility (68.4%), irritability (62.9%), and racing thought (61.5%) are more common whereas becoming more social (19.8%) and increase interest in sex (24.8%) are reported less.[30] No statistical significant difference found for mean HAMD score or severity of depression between MDQ-positive and negative group in our study.

Limitations of the study

1. Small sample size
2. Being a cross sectional study, cause – effect relationship cannot be established with this study.
3. Other entities of soft bipolarity (e.g., atypical depression etc.) are not included in the study.
4. We selected patients with psychiatric indices known to be associated with bipolar disorder. Therefore, this data cannot infer risk of bipolarity in the general primary care patient.
5. The percentage of antidepressant related mood switching cannot be identified.
6. Patients are more likely to fail to remember past episodes of hypomania and collateral history was rarely obtained from an informant who may have remembered past episodes of hypomania.

CONCLUSION

About 6.67% of tertiary care patients with major depressive disorder on antidepressant treatment screened positive for bipolar disorder on MDQ. The diagnosis is confirmed by clinical interview taken according to DSM-5 criteria for bipolar disorder.The MDQ screened positive for bipolar disorder was associated with the earliest age onset of depressive episode and long lifetime duration of

depression, more suicide attempts and higher family history of bipolar disorder than MDQ screened negative. These factors should be taken into account when we screenfor bipolar disorder.Further studies evaluating the efficacy of screening approach to identify patients who could benefit from appropriate diagnosis and timely intervention are warranted.

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REFERENCES

1. Angst J. The bipolar spectrum. Br J Psychiatry. 2007;190: 189-191.
   https://doi.org/10.1192/bjp.bp.106.030957
2. Goodwin GM and Geddes JR. What is the heartland of psychiatry? Br J Psychiatry. 2007;191:189-191.
   https://doi.org/10.1192/bjp.bp.107.036343
3. Katzow JJ, Hsu DJ and Ghaemi SN. The bipolar spectrum: A clinical perspective. Bipolar Disord. 2003;5(6):436-442.
   https://doi.org/10.1046/j.1399-5618.2003.00068.x
4. Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RM, Petukhova M, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the national comorbidity survey replication. Arch Gen Psychiatry. 2007;64(5):543-552.
   https://doi.org/10.1001/archpsyc.64.5.543
5. Murray CJ and Lopez AD. The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability from Diseases, Injuries, and Risk Factors in 1990 and Projected to 2020. Boston: Lancet, Harvard School of Public Health; 1997. p. 144.
6. Akiskal HS, Bourgeois ML, Angst J, Post R, Möller H and Hirschfeld R. Re-evaluating the prevalence of and diagnostic composition within the broad clinical spectrum of bipolar disorders. J Affect Disord. 2000;59(Suppl 1):S5-S30.
   https://doi.org/10.1016/s0165-0327(00)00203-2
7. Hirschfeld RM, Calabrese JR, Weissman MM, Reed M, Davies MA, Frye MA, et al. Screening for bipolar disorder in the community. J Clin Psychiatry. 2003;64(1):53-59.
   https://doi.org/10.4088/jcp.v64n0111
8. Benazzi F. Bipolar II disorder: Epidemiology, diagnosis and management. CNS Drugs. 2007;21(9):727-740.
   https://doi.org/10.2165/00023210-200721090-00003
9. Lish JD, Dime-Meenan S, Whybrow PC, Price RA and Hirschfeld RM. The national depressive and manic-depressive association (DMDA) survey of bipolar members. J Affect Disord. 1994;31(4):281-294.
   https://doi.org/10.1016/0165-0327(94)90104-x
10. Hirschfeld RM, Lewis L and Vernik LA. Perceptions and impact of bipolar disorder: How far have we really come? Results of the national depressive and manic-depressive association 2000 survey of individuals with bipolar disorder. J Clin Psychiatry. 2003;64(2):161-174.
11. Berk M, Dodd S, Callaly P, Berk L, Fitzgerald P, De Castella AR, et al. History of illness prior to a diagnosis of bipolar disorder or schizoaffective disorder. J Affect Disord. 2007;103(1-3):181-186.

https://doi.org/10.1016/j.jad.2007.01.027

12. Seemüller F, Riedel M, Dargel S, Djaja N, Schennach-Wolff R, Dittmann S, et al. Bipolar depression: Spectrum of clinical pictures and differentiation from unipolar depression. Nervenarzt. 2010;81(5):531-538.

https://doi.org/10.1007/s00115-009-2850-x

13. Rihmer Z and Pestality P. Bipolar II disorder and suicidal behavior. Psychiatr Clin North Am. 1999;22(3):667-673.

https://doi.org/10.1016/s0193-953x(05)70101-5

14. Shi L, Thiebaud P and McCombs JS. The impact of unrecognized bipolar disorders for patients treated for depression with antidepressants in the fee-for-services California Medicaid (Medical) program. J Affect Disord. 2004;82(3):373-383.

https://doi.org/10.1016/j.jad.2004.03.009

15. Matza LS, Rajagopalan KS, Thompson CL and De Lissovoy G. Misdiagnosed patients with bipolar disorder: Comorbidities, treatment patterns, and direct treatment costs. J Clin Psychiatry. 2005;66(11):1432-1440.

https://doi.org/10.4088/jcp.v66n1114

16. Awad AG, Rajagopalan K, Bolge SC and McDonnell DD. Quality of life among bipolar disorder patients misdiagnosed with major depressive disorder. Prim Care Companion J Clin Psychiatry. 2007;9(3):195-202.

https://doi.org/10.4088/pcc.v09n0305

17. Hirschfeld RM. Bipolar spectrum disorder: Improving its recognition and diagnosis. J Clin Psychiatry. 2001;62(Suppl 14):5-9.

18. Phelps JR and Ghaemi SN. Improving the diagnosis of bipolar disorder: Predictive value of screening test. J Affect Disord. 2006;92(2-3):141-148.

https://doi.org/10.1016/j.jad.2006.01.029

19. Hirschfeld RM, Williams JB, Spitzer RL, Calabrese JR, Flynn L, Keck PE Jr., et al. Development and validation of a screening instrument for bipolar spectrum disorder: The mood disorder questionnaire. Am J Psychiatry. 2000;157(11):1873-1875.

https://doi.org/10.1176/appi.ajp.157.11.1873

20. Available from: https://www.psychcongress.com/saundras-corner/scales-screeners/depression/hamilton-depression-rating-scale-ham-d. last accessed on 28/09/2021.

21. Smith DJ, Griffiths E, Kelly M, Hood K, Craddock N and Simpson SA. Unrecognised bipolar disorder in primary care patients with depression. Br J Psychiatry. 2011;199(1):49-56.

https://doi.org/10.1192/bjp.bp.110.083840

22. Hughes T, Cardno A, West R, Marino-Francis F, Featherstone I, Rolling K, et al. Unrecognised bipolar disorder among UK primary care patients prescribed antidepressants: An observational study. Br J Gen Pract. 2016;66(643):e71-e77.

https://doi.org/10.3399/bjgp16X683437

23. Kamat SA, Rajagopalan K, Pethick N, Willey V, Bullano M and Hassan M. Prevalence and humanistic impact of potential misdiagnosis of bipolar disorder among patients with major depressive disorder in a commercially insured population. J Manag Care Pharm. 2008;14(7):632-642.

24. Bouchra O, Maria S and Abderazak O. Screening of the unrecognised bipolar disorders among outpatients with recurrent depressive disorder: A cross-sectional study in psychiatric hospital in Morocco. Pan Afr Med J. 2017;27:247.

https://doi.org/10.11604/pamj.2017.27.247.8792

25. Shabani A, Zolfigol F and Akbari M. Brief major depressive episode as an essential predictor of the bipolar spectrum disorder. J Res Med Sci. 2009;14(1):29-35.

26. Angst J, Gamma A, Benazzi F, Ajdacic V, Eich D and Rössler W. Toward a re-definition of sub threshold bipolarity: Epidemiology and proposed criteria for bipolar-II, minor bipolar disorders and hypomania. J Affect Disord. 2003;73(1-2):133-146.

https://doi.org/10.1016/s0165-0327(02)00322-1

27. Post RM, Denicoff KD, Leverich GS, Altshuler LL, Frye MA, Suppes TM, et al. Morbidity in 258 bipolar outpatients followed for 1 year with daily prospective ratings on the NIMH life chart method. J Clin Psychiatry. 2003;64(6):680-690.

https://doi.org/10.4088/jcp.v64n0610

28. Chiu JF and Chokka PR. Prevalence of bipolar disorder symptoms in primary care (ProBiD-PC): A Canadian study. Can Fam Physician. 2011;57(2):e58-e67.

29. Benazzi F. Bipolar II disorder family history using the family history screen: Findings and clinical implications. Compr Psychiatry. 2004;45(2):77-82.

https://doi.org/10.1016/j.comppsych.2003.12.003

30. Hirschfeld RM, Cass AR, Holt DC, Carlson CA. Screening for bipolar disorder in patients treated for depression in a family medicine Clinic. J Am Board Fam Pract. 2005;18(4):233-239.

https://doi.org/10.3122/jabfm.18.4.233

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