Original Article

Sociodemographic and Clinical Predictors of Response in Manic Episodes: A Naturalistic, Prospective, Cohort Study

Jasmin Garg, Ajeet Sidana, B. S. Chavan, Shikha Goel

ABSTRACT

Background: Response to treatment of a manic episode is dependent on several sociodemographic and clinical factors as reported by researchers from other countries. The prescription of mood stabilizers and/or antipsychotics for manic episode depends on these factors. There is a lack of availability of data from India on this topic. Hence, this study was planned to identify the predictors of pharmacological response. **Materials and Methods:** Forty-two patients with a diagnosis of bipolar affective disorder current episode manic were enrolled and assessed for sociodemographic variables and clinical variables such as age of onset, family history, comorbidities, index episode, and number of past episodes. They were divided into four groups depending on the treatment they were receiving, namely, lithium with an antipsychotic ($n = 25$), lithium with divalproex and an antipsychotic ($n = 8$), divalproex with an antipsychotic ($n = 5$), and the miscellaneous group ($n = 4$). The primary outcome measure was improvement in the Young Mania Rating Scale score and secondary outcome measure was duration of ward stay. **Results:** There was a significant improvement in all the treatment modalities and it was comparable. There was no significant impact of any sociodemographic or clinical variable on treatment outcome except that females had significantly better response than males. There was nearly significant shorter duration of hospitalization in the lithium and antipsychotics groups compared to divalproex group. **Conclusion:** All treatment modalities are equally efficacious in the management of manic episode in short term. However, lithium and antipsychotics tend to produce early response than divalproex. Other sociodemographic and clinical predictors were not significantly associated with response.

Key words: *Bipolar disorder, manic episode, predictors, response*

INTRODUCTION

Bipolar disorder is a chronic debilitating psychiatric illness which is episodic in nature. The patients present with episodes of mania, depression, or of mixed type. The worldwide lifetime prevalence ranges from 1.3% to 3.1%.[1] Patients presenting with manic episodes often

Access this article online	
Website: www.ijpm.info	Quick Response Code
DOI: 10.4103/IJPSYM.IJPSYM_418_16	

How to cite this article: Garg J, Sidana A, Chavan BS, Goel S. Sociodemographic and clinical predictors of response in manic episodes: A naturalistic, prospective, cohort study. Indian J Psychol Med 2017;39:584-9.

Department of Psychiatry, Government Medical College and Hospital, Chandigarh, India

Address for correspondence: Dr. Jasmin Garg
Department of Psychiatry, Government Medical College and Hospital, Sector 32, Chandigarh - 160 030, India.
E-mail: jasmin.arneja@gmail.com

require hospitalization for acute management. Most clinical practice guidelines recommend that the mainstay of management of an acute episode of mania is a mood stabilizer with or without antipsychotics.[2] Mood stabilizers used in combination with antipsychotics are reported to have early response.[3] Studies from India showed that lithium is the preferred mood stabilizer prescribed to patients as compared to anticonvulsant mood stabilizers.[4]

There is abundant literature available from Western countries about the predictors of response on lithium and other mood stabilizers. Some studies have reported that a later age of onset of illness, less number of prior episodes, a pattern of mania-depression-euthymia, and family history of bipolar disorder were associated with better response to lithium.[1] Others have described that patients with comorbid alcohol dependence and history of mixed episodes or rapid cycling have lesser response to lithium but better response to anticonvulsant mood stabilizers.[5-8] An association has also been described between the socio-occupational dysfunction and poorer outcome in bipolar disorder.[9]

There are certain differences in the presentation and course of bipolar disorder in developing countries when compared to Western countries. For example, research from Western literature states that there are more depressive episodes than manic episodes in the lifetime of a patient with bipolar disorder. However, Indian studies reported that, in patients with bipolar disorder, there are more manic episodes.[10,11] There is scarcity of research on the predictors of response of acute manic episode from India. It is not known whether the same predictors such as age of onset, number of prior episodes, family history, poor socio-occupational functioning, and education would be applicable in Indian population.

Hence, this study was planned to assess the psychosocial and clinical predictors of response in manic episodes on various mood stabilizers and antipsychotics.

MATERIALS AND METHODS

Patient selection

This study was carried out in the department of psychiatry of a tertiary care center of North India. The department is running a general hospital psychiatric unit for acute short-term admission and care of patients with mental illness.

Inclusion criteria

Inpatients suffering from bipolar affective disorder according to the International Classification of Diseases-10 were enrolled in the study from March to July 2016.[12] Patients were admitted to ward by the decision of treating consultants. The criteria for admission were when a patient is unmanageable at home due to excessive aggression or violence and/or poses a risk to self or others due to mental illness. The patients were in the age range of 18–65 years, both males and females and had given informed consent for the study.

Exclusion criteria

The patients admitted with depressive, mixed episode or first manic episode were excluded from the study. In addition, those who had associated mental retardation, pregnancy/lactation, or presence of uncontrolled medical or surgical condition were excluded from the study. Patients who were advised electroconvulsive therapy (ECT) or those acutely suicidal were also excluded from the study. Those with comorbid psychiatric illnesses except substance abuse were also excluded from the study.

The confidentiality of the information obtained was maintained, and the principles enunciated in the Declaration of Helsinki were complied, and the Indian Council of Medical Research guidelines on biomedical research on humans were followed.[13,14]

Treatment protocol

It was a naturalistic study, and the enrolled patients were prescribed various mood stabilizers and antipsychotics according to the clinical need of patient by the treating psychiatrist. It was tried to restart or optimize the same pharmacological treatment the patient was earlier on. If a patient was on antidepressants, it was stopped. Depending on the type of treatment advised by the consultant psychiatrist, the sample was divided into the following four groups.

Group A (lithium with antipsychotics), Group B (lithium and divalproex sodium), Group C (divalproex sodium with antipsychotics), and Group D (miscellaneous). The Group D included the patients who were administered tablet carbamazepine with atypical antipsychotics and those who were given atypical antipsychotics only without mood stabilizers.

The serum lithium levels were maintained at 0.7–1.2 mEq/L and valproate levels between 80 and 120 mcg/ml. Patients were also monitored on other blood and urine investigations which were electrolytes, renal function tests, liver function tests, hemogram, blood sugar, lipid profile, thyroid function tests, and electrocardiogram for initiating a treatment regimen and its continuation. They were also administered benzodiazepines for short term for the purpose of sedation and trihexyphenidyl in case of extrapyramidal

symptoms. It was planned to exclude those patients who had severe intolerable side effects, but none of the patients dropped due to intolerable side effects.

Assessment tools

The sociodemographic data of enrolled patients were recorded along with clinical parameters such as duration of current episode, total duration of illness, family history of bipolar disorder, history of substance abuse (excluding caffeine and nicotine), and comorbid illnesses.

The Young Mania Rating Scale (YMRS) was administered on the day of admission to assess the severity of episode and just before discharge to record the improvement in manic symptoms.[15] Duration of hospitalization was also noted for assessing the response. The decision about discharge is dependent on the control of symptoms to such an extent that the patient becomes manageable at home by family members, there is minimal risk to self or others, and there is acceptance of oral medications regardless of complete remission or development of good insight into the illness. It is decided by the treating consultant to discharge the patient, and the duration of ward stay is usually around 20 days.

Statistical analysis

Statistical analysis was carried out using SPSS for Windows, Version 16.0 (SPSS Inc., Chicago, 2007). Chi-square test, Kruskal–Wallis test, and Wilcoxon signed-rank test were done for analysis of nonparametric data. Statistical significance was defined as $P < 0.5$. For assessing the impact of age of onset, two groups were formed defined by onset at age <30 years and >30 years. Similarly, for the number of past episodes, two groups were made, less than or more than 10.

RESULTS

A total of 57 patients of bipolar disorder were admitted in psychiatry ward during this period and enrolled for study. A total of 15 patients were excluded from the study due to various reasons as nine had current episode depressive or mixed or first manic episode, two received ECT for the current episode, three were excluded due to early discharge on request, and one patient was excluded due to associated uncontrolled cardiac illness [Figure 1].

Majority of patients ($n = 25$) were prescribed lithium in combination with an antipsychotic (Group A); eight patients received combination of lithium, divalproex sodium, and an antipsychotic (Group B); five patients received divalproex with antipsychotic (Group C); and four patients were in miscellaneous group who received other mood stabilizers or antipsychotics alone (Group D). The various antipsychotics prescribed were risperidone ($n = 19$), olanzapine ($n = 10$), quetiapine ($n = 5$), clozapine (1), chlorpromazine ($n = 2$), and haloperidol ($n = 2$).

A total of 42 patients were included in the final analysis. Their sociodemographic characteristics are shown in Table 1. The mean age at inclusion was 38.38 ± 13.22 years, the mean total duration of illness was 11.45 ± 9.84 years, and the mean age at onset was 26.90 ± 9.60 years. The duration of current manic episode was approximately 2 months (mean ± standard deviation, 1.78 ± 1.64). The mean YMRS score on admission and discharge was 30.98 ± 8.78 and 15.31 ± 8.84, respectively. The mean duration of ward stay was 22.10 ± 12.69 days. The sociodemographic and clinical characteristics were compared on YMRS score at baseline and discharge [Table 1].

Majority of baseline sociodemographic and clinical variables were comparable on YMRS score except gender and severity of manic episode. There was a statistically significant difference between the baseline YMRS in males and females which became nonsignificant at discharge. Hence, females had better response to treatment than males. The mean YMRS score was significantly higher in the group "manic with psychotic symptoms" than "manic without psychotic symptoms," both at baseline and endpoint. Then, mean difference between these two groups was calculated and compared which came out to be statistically nonsignificant ($P = 0.602$), which meant that there was comparable improvement in both manic with or without psychotic symptoms groups.

The improvement in YMRS score was compared among the pharmacological treatment groups and no significant difference was found. Response was also assessed on the basis of duration of hospitalization, but there was no significant difference between the groups [Table 2].

Duration of ward stay was longer in Group C (divalproex with antipsychotic) compared to Group A (lithium with

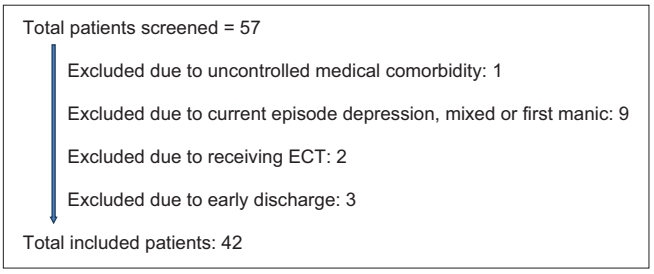

Figure 1: Patient flow chart

Table 1: Socio-demographic and clinical variables with comparison on baseline

Variable	Number of patients (%) *N*=42	YMRS on admission, Mean±SD	*P*	YMRS on discharge, Mean±SD	*P*
Gender					
Males	26 (61.9)	28.65±9.45	0.013*	14.96±8.32	0.775
Females	16 (38.10)	34.75±6.09		15.87±9.86	
Locality					
Urban	26 (61.9)	29.69±8.42	0.227	13.42±6.84	0.180
Rural	16 (38.10)	33.06±9.21		18.37±10.91	
Socioeconomic status					
Lower	23 (54.76)	32.78±9.94	0.198	17.17±9.74	0.428
Middle	16 (38.1)	28.28±7.11		13.12±7.53	
Upper	3 (7.14)	32±3.60		12.66±6.42	
Marital status					
Married	28 (66.67)	31.07±8.57	0.852	16.07±8.96	0.227
Single	14 (33.33)	30.78±9.50		13.78±8.70	
Education					
Graduate	9 (21.43)	31.15±9.96	0.831	16.76±10.49	0.817
Matric	13 (30.95)	29.77±6.26		12.77±6.18	
Primary	13 (30.95)	30.76±9.66		15.92±9.41	
Illiterate	7 (16.67)	32.57±9.16		14.71±8.34	
Age of onset in years					
< 30 years	26 (61.90)	31.19±8.87	0.846	15.73±9.66	0.896
≥ 30 years	16 (38.09)	30.62±8.89		16.62±7.53	
Comorbidity (medical/surgical)					
Present	12 (26.19)	31.09±8.54	0.645	14.18±6.33	0.685
Absent	30 (71.42)	30.93±8.99		15.70±9.62	
Substance dependence					
Present	9 (21.43)	31.33±9.36	0.690	16.88±10.62	0.517
Absent	33 (78.57)	30.87±8.76		14.87±8.42	
Manic episode type					
With psychotic symptoms	24 (57.14)	35.62±7.15	0.000***	19.25±9.58	0.001**
Without psychotic symptoms	18 (42.85)	24.77±6.74		10.05±3.58	
Family history of psychosis or bipolar disorder					
Present	12 (28.57)	30.91±10.06	0.900	17.16±8.21	0.145
Absent	30 (71.42)	31±8.39		14.56±9.09	
Index episode					
Depressive	7 (16.67)	28.42±6.02	0.318	16.34±9.20	0.100
Manic	35 (83.33)	31.48±9.21		10.14±4.01	
No. of past episodes					
<10	34 (80.95)	31.37±9.33	0.477	11.71±3.86	0.435
≥10	8 (19.04)	29±5.25		16.02±9.39	

YMRS: Young Mania Rating Scale, *$P<0.05$, **$P<0.005$, ***$P<0.0005$

Table 2: Effect of pharmacological treatment on YMRS and duration of ward stay

Group	*N* (%)	Mean±SD		
		YMRS at baseline	YMRS at discharge	Duration of ward stay in days
A (Lithium with antipsychotic)	25 (59.52)	30.68±9.35	15.08±8.66	19.68±9.67
B (Lithium with Divalproex)	8 (19.05)	30.25±9.22	16±7.42	24.87±15.64
C (Divalproex with antipsychotic)	5 (11.90)	31±5.47	15±9.11	35±18.47
D (Miscellaneous)	4 (9.52)	34.25±9.91	15.75±14.97	15.5±4.65
Intergroup *P* value	0.856 (Chi square 0.744)			0.190 (Chi square 4.761)

antipsychotic) and Group D (miscellaneous) with $P = 0.066$ and $P = 0.05$, respectively. There was no significant difference in the duration of ward stay and improvement in YMRS scores in rest of the groups.

DISCUSSION

Findings of the present study show that the improvement in manic symptoms is not influenced by psychosocial

factors and clinical factors including type of index episode or different mood stabilizers. All modalities of treatment were found to be equally effective. It is in contrary to the research from other countries in which it has been shown that there are several sociodemographic, clinical, and pharmacological predictors of a response in manic episodes.[1,5,9,16-19]

In this study, treatment outcomes did not depend on the socioeconomic status, education, marital status, and employment status. However, a poorer baseline psychosocial functioning depicted by unemployment, being single or divorced, has been associated with poorer response in bipolar disorder.[9,16] In the present study, the response in manic episode among females was statistically better than males. Although no gender-wise difference in response to treatment has been reported in literature, it has been documented that men suffer more and have higher severity of manic episodes than women.[20,21]

Regarding locality of patients, no significant difference was found between urban and rural population. An earlier Indian study has described the pattern and course of bipolar disorder in rural population, but a comparison of course between urban and rural population was not carried out in that study.[22]

In the current study, approximately, 21% had comorbid substance dependence and 26% had medical comorbidity. This was similar to the findings of another Indian study which looked into the associated comorbidities in bipolar disorder.[23] A significant association of these comorbidities in the outcome of manic episode could not be found in the present study though it has been reported to be a poor prognostic factor in another study.[5]

Furthermore, no difference could be found in treatment response due to age of onset of bipolar disorder, presence of associated psychotic symptoms, and number of past episodes. Studies have described that a later age of onset has been associated with good response and more number of past episodes, severe symptoms carry risk for poor response with both lithium and divalproex.[1,17-19]

Among various pharmacological groups, though the response in manic episode was comparable on the basis of improvement in YMRS scores, the patients treated with lithium and atypical antipsychotics were more likely to be discharged early compared to the patients on divalproex sodium and antipsychotics. The duration of ward stay was longer in the divalproex group and it was approaching significant levels. This finding is contrary to the earlier reports that divalproex tends to produce early response than lithium.[3]

Regarding the course of bipolar disorder, it was tried to look into the index episode of patients, and majority had manic episode. A correlation has been described in literature that a pattern of depression-mania-euthymia has poorer response to lithium.[1] Though we could not look into this pattern directly, according to the findings of the present study, no correlation could be found between index episode and response.

Strengths of the study

This study was carried out in real world and was a naturalistic observational study. Patients were assessed comprehensively on several sociodemographic and clinical variables which have known impact on the response of a manic episode. Patients were hospitalized during the entire study period, hence compliance was ensured.

However, there were some limitations in the study. Effect of some other important clinical variables could not be seen due to lesser number of patients. In addition, in the pharmacological groups, the mood stabilizers were combined with antipsychotics for early response, so it is not known whether the antipsychotics led to improvement or mood stabilizers.

Nevertheless, this is the first of its kind study from India, and the findings of this study show that response of a patient in manic episode is independent of psychosocial factors, and a combination of lithium or valproate with antipsychotics is equally efficacious. Early response is more likely when treated with lithium as compared to treatment with divalproex sodium. Further studies can be carried out with larger sample size and longer duration for affirming the findings of the current study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Tighe SK, Mahon PB, Potash JB. Predictors of lithium response in bipolar disorder. Ther Adv Chronic Dis 2011;2:209-26.
2. Saddichha S, Chaturvedi SK. Clinical practice guidelines in psychiatry: More confusion than clarity? A critical review and recommendation of a unified guideline. ISRN Psychiatry 2014;2014:828917.
3. Awasthi A, Kumar S, Vikas A. Clinical Practice Guidelines for the Management of Bipolar Affective (Mood) Disorders. IPS Guideline Committee on Bipolar Affective Disorders; 2005.

4. Trivedi JK, Sareen H, Yadav VS, Rai SB. Prescription pattern of mood stabilizers for bipolar disorder at a tertiary health care centre in North India. Indian J Psychiatry 2013;55:131-4.
5. Sportiche S, Geoffroy PA, Brichant-Petitjean C, Gard S, Khan JP, Azorin JM, *et al.* Clinical factors associated with lithium response in bipolar disorders. Aust N Z J Psychiatry 2016. pii: 0004867416664794.
6. Keck PE Jr., Nabulsi AA, Taylor JL, Henke CJ, Chmiel JJ, Stanton SP, *et al.* A pharmacoeconomic model of divalproex vs. lithium in the acute and prophylactic treatment of bipolar I disorder. J Clin Psychiatry 1996;57:213-22.
7. Calabrese JR, Fatemi SH, Kujawa M, Woyshville MJ. Predictors of response to mood stabilizers. J Clin Psychopharmacol 1996;16 2 Suppl 1:24S-31S.
8. Backlund L, Ehnvall A, Hetta J, Isacsson G, Agren H. Identifying predictors for good lithium response – A retrospective analysis of 100 patients with bipolar disorder using a life-charting method. Eur Psychiatry 2009;24:171-7.
9. Deckersbach T, Nierenberg AA, McInnis MG, Salcedo S, Bernstein EE, Kemp DE, *et al.* Baseline disability and poor functioning in bipolar disorder predict worse outcomes: Results from the Bipolar CHOICE study. J Clin Psychiatry 2016;77:100-8.
10. Rangappa SB, Munivenkatappa S, Narayanaswamy JC, Jain S, Reddy YC. Predominant mania course in Indian patients with bipolar I disorder. Asian J Psychiatr 2016;22:22-7.
11. Karthick S, Kattimani S, Rajkumar RP, Bharadwaj B, Sarkar S. Long term course of bipolar I disorder in India: Using retrospective life chart method. J Affect Disord 2015;173:255-60.
12. World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders- Clinical Descriptions and Diagnostic Guidelines. Geneva: World Health Organization; 2007.
13. Williams JR. The declaration of Helsinki and public health. Bull World Health Organ 2008;86:650-2.
14. Indian Council Medical Research. Ethical Guidelines for Biomedical Research on Human Participants. New Delhi: Indian Council Medical Research; 2006.
15. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: Reliability, validity and sensitivity. Br J Psychiatry 1978;133:429-35.
16. Yazici O, Kora K, Uçok A, Tunali D, Turan N. Predictors of lithium prophylaxis in bipolar patients. J Affect Disord 1999;55:133-42.
17. Kleindienst N, Engel R, Greil W. Which clinical factors predict response to prophylactic lithium? A systematic review for bipolar disorders. Bipolar Disord 2005;7:404-17.
18. Welge JA, Keck PE Jr., Meinhold JM. Predictors of response to treatment of acute bipolar manic episodes with divalproex sodium or placebo in 2 randomized, controlled, parallel-group trials. J Clin Psychopharmacol 2004;24:607-12.
19. Lipkovich IA, Houston JP, Ahl J. Identifying patterns in treatment response profiles in acute bipolar mania: A cluster analysis approach. BMC Psychiatry 2008;8:65.
20. Ram D, Ram D. Subsyndromal states in bipolar disorder. Indian J Psychiatry 2010;52:367-70.
21. Diflorio A, Jones I. Is sex important? Gender differences in bipolar disorder. Int Rev Psychiatry 2010;22:437-52.
22. Chopra MP, Kishore Kumar KV, Subbakrishna DK, Jain S, Murthy RS. The course of bipolar disorder in rural India. Indian J Psychiatry 2006;48:254-7.
23. Munoli RN, Praharaj SK, Sharma PS. Co-morbidity in bipolar disorder: A retrospective study. Indian J Psychol Med 2014;36:270-5.