

A Cross-sectional Analysis of Patterns and Predictors of Medication Adherence in Bipolar Disorder: Single Center Experience from South India

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Objective: Our objective was to determine patterns and predictors of medication adherence in bipolar disorder.

Methods: Between August 2015 and December 2016, we recruited 160 patients with a diagnosis of bipolar disorder as per International Classification of Diseases-10: Clinical Descriptions and Diagnostic Guidelines. The diagnosis was further confirmed by using the MINI International Neuropsychiatric Inventory. All of them were currently in remission (confirmed by standard measures) and on stable dosing of medication for at least a year. Medication adherence was assessed using Tamil validated version of Morisky Medication Adherence Scale. Patients were dichotomized into low adherence (<6) and high adherence (≥ 6) groups and compared on various socio-demographic and clinical variables.

Results: Majority of the sample (n=97, 60.6%) demonstrated low adherence to treatment regimen. Being employed and having spent greater number of days in hospital were predictive of higher medication adherence (odds ratio [OR] 2.78, 95% confidence interval [CI] 1.019-7.585; and OR 1.02, 95% CI 1.003-1.037, respectively). Fewer number of lifetime depressive episodes and positive drug attitudes demonstrated trend level positive association with high medication adherence.

Conclusion: Non-adherence to prescribed medications is a common problem in bipolar disorder. Interventions targeting vocation, medication focused psychoeducation and promotion of positive drug attitudes are likely to enhance medication adherence in this group.

KEY WORDS: Bipolar disorder; Medication adherence; Medication compliance; Medication persistence; Therapeutics; Psychiatry.

INTRODUCTION

The World Health Organization has defined treatment adherence as: "The extent to which a person's behavior—taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a healthcare provider".¹⁾ Bipolar disorder (BD) is a highly prevalent, chronic and disabling condition. Among the many unmet needs in managing this condition, improving adherence to medications is a clear and

present challenge to health care providers.^{2,3)} In a widely quoted study on 13-year outcomes in BD, the authors found that bipolar subjects spent about 32% of time in clinically significant depression, 9% with manic symptoms and 6% with symptoms from both poles.⁴⁾ Medication non-adherence is often a greater problem in psychiatric disorders as compared to other chronic medical conditions and has been postulated as a possible reason for the high residual symptom burden in BD.^{5,6)}

Existing literature suggests that about 20-60% of BD patients are non-adherent to their medication regimens.^{7,8)} Further, non-adherence has been shown to have a robust association with a variety of negative outcomes such as relapse, re-hospitalizations, sub-optimal functioning and suicidality in BD.⁹⁻¹¹⁾ Many authors also argue that non-adherence is the reason for the "efficacy-effectiveness" gap seen in BD, wherein an increased response to drug

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treatments is seen in clinical trials than in real world practice.^{12,13} Consequently, it is important to systematically investigate the determinants of medication adherence so that clinicians and health care providers can work on these factors to optimize management. A range of factors have been found to be predictive of non-adherence in bipolar subjects including concurrent alcohol use disorder, greater severity of depressive episodes, polypharmacy, negative attitudes towards medication, quality of doctor-patient relationship and decreased insight.^{7,8,14-17}

Evidence suggests that adherence is a complex behavior that is a result of an interaction of several variables such as patient attributes about illness, social context, access to treatment and service delivery^{1,18-20} which may presumably differ across cultures and settings. In this scenario, we carried out the present study with two objectives: first, to assess medication adherence patterns using a self-report measure validated in the local language and second, to identify predictors of medication adherence in BD among South Indian Tamil speaking population.

METHODS

The present cross-sectional study was carried out in the Department of Psychiatry in a teaching cum tertiary care hospital over a period of one and a half years from August 2015 to December 2016. The hospital is located in Puducherry, South India and Tamil is the local language. The study had prior approval from JIPMER Institute Human Ethics Committee via approval No. JIP/IEC/2015/16/603. Subjects were recruited from the weekly outpatient Mood Disorders Clinic run by the Department of Psychiatry. All patients with a mood spectrum disorder diagnosis, treated either on in-patient or out-patient basis, are eventually assigned to this clinic for getting their regular drug refills. Patients are asked to follow up once every three weeks for their regular check-up and refills of their medicines. Checkups and medicine refills are provided free of cost through governmental aid. Psychotropic agents stocked in the hospital pharmacy include three antipsychotics (haloperidol, chlorpromazine, and risperidone), three mood stabilizers (lithium, sodium valproate, and carbamazepine), two anti-depressants (fluoxetine and amitriptyline) and two anxiolytics (diazepam and clonazepam). These drugs are made available throughout the year for free dispensing in order to benefit the patients.

Consequently, nearly every patient in the follow-up clinic is managed with agents available from this basket of drugs. Presently, the clinic has about 400 to 500 patients on its rolls and diagnoses are made as per International Classification of Diseases-10: Clinical descriptions and diagnostic guidelines.²¹

The inclusion criteria for the present study were: patients in the age group 18-65 years with a file diagnosis of Bipolar Affective Disorder as per International Classification of Diseases-10: Clinical Descriptions and Diagnostic Guidelines (F31.0-F31.7).²¹ Additionally, the MINI International Neuropsychiatric Interview (MINI) was used to confirm the diagnosis.²² We included only patients on stable dosing of medications for the past one year and in clinical remission (Hamilton Depression Rating Scale [HDRS]²³ scores ≤ 7 /Young Mania Rating Scale [YMRS]²⁴ scores ≤ 8). All such patients, who were registered into the follow-up clinic for continued care, were screened for eligibility regardless of their compliance with prescribed drugs. Those on stable dosing of medications were selected as it was deemed unethical to include other patients. Participants were selected by convenient sampling from the outpatient Department of Psychiatry after applying the inclusion/exclusion criteria and obtaining written informed consent for participation.

Basic and relevant socio-demographic data was collected using a semi-structured proforma. Details about physical and psychiatric co-morbidity were collected from patient and informant interviews as well as verified from available records. Subsequently, all patients were rated on the following measures;

1. Morisky Medication Adherence Scale (MMAS)-8²⁵: This is a structured, widely used, self-reported measure for medication adherence, the primary outcome measure for this study. It has better psychometric properties than the 4-item Morisky, Green and Levine adherence scale, particularly a higher internal consistency (Cronbach's alpha of 0.83 vs. 0.61).^{25,26} The scale has been used for a range of chronic health conditions, including BD.^{27,28} For the study, we obtained permission to use the Tamil translated and validated version of MMAS-8. The scale consists of eight questions. The first seven elicit a dichotomous reply (yes/no) and the last one is answered using a 5-point Likert Scale. Total score ranges from 0 to 8 with three categories—low adherence (< 6), medium adherence (≥ 6 but < 8) and high adherence (score of 8). Since only very few pa-

tients (n=12) reported high adherence, we dichotomized the dependent variable into two groups—low adherence (score <6) and high adherence (score ≥6).

2. Drug Attitudes Inventory (DAI)-10²⁹: This is a 10-item shorter version of the original DAI-30 designed to assess attitudes, experiences and beliefs about psychiatric medications. Each item is designed to elicit a dichotomous response (true or false). Some items are reverse scored. Total score is obtained by summing the individual items and ranges from -10 to +10. Patients were categorized as having negative attitudes (total score <10) or positive attitudes (total score >10) in line with the original scoring method.³⁰

Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 20 (IBM Co., Armonk, NY, USA). Baseline socio-demographic and clinical variables were represented as mean with standard deviation and frequencies and percentages for continuous and categorical data respectively. They were compared between the low and high medication adherence groups (defined earlier) in the univariate analysis. Strength of these comparisons was measured with non-parametric Mann-Whitney *U* test or Student *t* test for non-normal and normally distributed variables respectively and chi-square test for discrete variables. Normality was assessed using the Shapiro-Wilk test. For identifying predictors of medication adherence, variables which showed at least a trend level significance in the univariate analysis ($p < 0.10$) were entered into the backward logistic regression model. This method, where all variables are entered into the model in the first step and then sequentially deleted, was used as the study was exploratory in nature and gives more chance for variables to remain in the final regression equation. All statistical analyses were carried out for two-tailed significance and a $p < 0.05$ was considered significant for all univariate and multivariate comparisons.

RESULTS

The sample comprised of 160 patients with BD. The mean age of the sample was 37.8±10.8 years (range, 18-64 years). The mean age of males was 37.7±11.3 years and females were 37.9±10.4. Males (50.6%) and females (49.4%) were nearly equally represented in the sample.

Majority of the sample (72.5%) were married and had studied till tenth grade (68.1%). The total number of lifetime episodes varied from 1 to 20. Overall, there were more lifetime manic episodes (mean, 3.4; standard deviation [SD], 2.6) than depressive (mean, 0.7; SD, 1.4). Nearly three-fourth of the sample (n=118, 73.8%) had received in-patient care for their mood episodes at least once during the course of their illness. The other baseline characteristics are shown in Table 1.

Table 1. Baseline socio-demographic characteristics of the entire sample

Variable	Data
Age (yr)	
18-25	23 (14.4)
26-35	46 (28.8)
36-45	52 (32.5)
46-55	29 (18.1)
≥56	10 (6.3)
Sex	
Male	81 (50.6)
Female	79 (49.4)
Marital status	
Married	116 (72.5)
Single	44 (27.5)
Education	
≤10th grade	109 (68.1)
>10th grade	51 (31.9)
Occupation	
Employed	87 (54.4)
Not employed	73 (45.6)
Current substance dependence*	
Yes	18 (11.3)
No	140 (87.5)
Family history of psychiatric illness	
Yes	69 (43.1)
No	91 (56.9)
History of chronic medical illness	
Yes	35 (21.9)
No	125 (78.1)
Duration of illness (yr)	13.0±8.6
Age at onset (yr)	24.8±8.4
Lifetime episodes	4.1±3.1
Manic episodes	3.4±2.6
Depressive episodes	0.7±1.4
In-patient admissions	1.7±1.9
Total of hospital days	48.7±66.8
YMRS score	0.43±0.7
HDRS score	0.96±0.9
Drug Attitudes Inventory score	7.5±2.1

Values are presented as number (%) or mean±standard deviation. YMRS, Young Mania Rating Scale; HDRS, Hamilton Depression Rating Scale.

*Data missing for two cases.

With regard to concurrent physical illness, diabetes mellitus was the single most common medical co-morbidity (n=22) followed by systemic hypertension (n=6), hypothyroidism (n=5), bronchial asthma (n=4), tuberculosis (n=2), obesity (n=1) and psoriasis (n=1). Overall, 35 patients (21.9%) had a history of chronic medical illness of whom six patients had multiple medical co-morbidities. All patients diagnosed with diabetes in our sample were on oral hypoglycemic agents (either tablet [Tab.] metformin alone [1,000-1,500 mg per day] or combination of Tab. metformin plus Tab. glibenclamide). Two of the patients diagnosed with systemic hypertension

were on calcium channel blockers (Tab. amlodipine 5 mg) while others were not taking any treatment for the same. Similarly, none of the bronchial asthma patients were on any long term medications while all patients with hypothyroidism were on replacement thyroxin therapy (50-100 µg per day). Both the patients with tuberculosis had recovered and were not on any active treatment for the same. No treatment details were available for five patients. Regarding psychiatric co-morbidity, 18 patients (11.3%) fulfilled criteria for substance dependence while another 10 patients (6.3%) were using substances in a harmful manner. Two patients (1.3%) had evidence of

Table 2. Correlates of medication adherence

Variable	High adherence group (n=63)	Low adherence group (n=97)	Comparison (<i>p</i> value)
Age (yr)	38.3±10.9	36.9±10.7	<i>t</i> =-0.779 (0.437)
Gender			$\chi^2=0.465$ (0.495)
Male	34 (56)	47 (48.5)	
Female	29 (44)	50 (51.5)	
Marital status			$\chi^2=0.014$ (0.906)
Married	46 (73.0)	70 (72.2)	
Single	17 (27.0)	27 (27.8)	
Education			$\chi^2=0.444$ (0.505)
≤10th grade	41 (65.1)	68 (70.1)	
>10th grade	22 (34.9)	29 (29.9)	
Occupation			$\chi^2=3.482$ (0.062)
Employed	40 (63.5)	47 (48.5)	
Not employed	23 (36.5)	50 (51.5)	
Substance dependence*			$\chi^2=1.120$ (0.290)
Yes	5 (7.9)	13 (13.4)	
No	57 (90.5)	83 (85.6)	
Family history of psychiatric illness			$\chi^2=0.358$ (0.550)
Yes	29 (46.0)	40 (41.2)	
No	34 (54.0)	57 (58.8)	
History of chronic medical illness			$\chi^2=1.185$ (0.276)
Yes	11 (17.5)	24 (24.7)	
No	52 (82.5)	73 (75.3)	
Polypharmacy			$\chi^2=0.215$ (0.643)
Yes	36 (57.1)	59 (60.8)	
No	27 (42.9)	38 (39.2)	
Duration of illness (yr)	12.9±9.6	13.1±7.9	<i>U</i> =2,901.00 (0.589)
Age at onset (yr)	24.0±8.0	25.3±8.6	<i>U</i> =2,823.50 (0.417)
Lifetime episodes	3.8±2.9	4.2±3.2	<i>U</i> =2,768.00 (0.306)
Manic episodes	3.2±2.6	3.5±2.6	<i>U</i> =2,757.00 (0.287)
Depressive episodes	0.4±0.8	0.8±1.7	<i>U</i> =2,742.50 (0.240)
In-patient admissions	1.7±1.8	1.8±1.9	<i>U</i> =3,014.50 (0.883)
Total of hospital days	51.4±58.2	46.9±72.0	<i>U</i> =2,785.00 (0.340)
YMRS score	0.51±0.7	0.38±0.7	<i>U</i> =2,725.50 (0.168)
HDRS score	0.86±0.9	1.02±0.9	<i>U</i> =2,776.50 (0.302)
Drug Attitudes Inventory score	8.0±1.7	7.2±2.3	<i>t</i> =2.165 (0.032)*

Values are presented as mean ± standard deviation or number (%).

YMRS, Young Mania Rating Scale; HDRS, Hamilton Depression Rating Scale.

*Data missing for two cases.

Comparisons made using Student *t* test (*t*) or chi-square (χ^2) or Mann-Whitney *U* test (*U*); **p*<0.05.

paranoid personality traits. No psychiatric co-morbidity was found in the remaining sample (n=130, 81.3%).

Ninety-seven patients (60.6%) demonstrated low adherence to the treatment regimen. Medium adherence was noted in 51 patients (31.9%) while only 12 patients (7.5%) had high adherence. Next, we conducted a univariate analysis to identify variables that differed between the dichotomized medication adherence groups (Table 2). It was observed that none of the socio-demographic or clinical variables differed between the groups apart from drug attitude scores which were higher (reflecting more positive attitudes) in the high medication adherence group. Further, the residual mood state (measured using HDRS and YMRS scales) did not distinguish between the high and low medication adherence groups (Table 2).

Subsequently, we did a multivariate analysis using binary logistic regression to find out the predictors of high medication adherence (dependent variable). Co-variables studied included age, gender, occupational status and illness characteristics such as total number of lifetime episodes, number of manic episodes, number of depressive episodes and total number of days spent in hospitalization. Most of these co-variables had a $p < 0.3$ in the univariate analysis and hence were included in the regression model. Drug attitudes were also included as a co-variate as it had emerged significant in the univariate analysis. Table 3 summarizes the results of the regression analysis. It was observed that occupational status and length of hospital stay were predictive of high medication adherence. Drug attitude scores and number of depressive episodes had a positive and negative trend level association with high medication adherence respectively. These variables put together explained 22.6% of the variance in medication adherence (Nagelkerke R square of model=0.226). Hosmer-Lemeshow goodness of fit statistic was 5.498 ($p=0.703$) indicating that the regression

model was acceptable.

DISCUSSION

The present study found that majority of patients (60.6%) with BD had low adherence to their medication regimen and this is roughly consistent with previous studies in this disorder.^{28,31,32} Only very few patients (7.5%) in our study were fully adherent. Taking into account the fact that this was a naturalistic descriptive study, the results are a grim reminder that non-adherence continues to be a major issue among bipolar subjects. Clinicians need to consider this when planning management as non-adherence to medications can compromise clinical outcomes. Majority of our sample (n=93, 58.1%) were on two psychotropic agents (most commonly mood stabilizer plus antipsychotic) and very few were on more than two agents (n=3, 1.9%). Hence, we could not examine potential relationships between increasing treatment regimen complexity and medication adherence. This is an area for further exploration.

Regarding predictors of medication adherence, we noted that those who had high adherence were likely to be employed and had spent higher number of days in the hospital across their admissions. Such individuals were also noted to have more positive attitudes towards their medications and had fewer lifetime depressive episodes though these two factors had a trend level significance. There is some variation in factors predictive of medication adherence in published literature on BDs. One study found an overrepresentation of young, unmarried and socially isolated individuals among bipolar patients who are non-adherent to medications³³ while another reported male gender, higher educational status, no substance use and monotherapy as factors associated with treatment adherence in this group.²⁸ Studies on non-association of adherence with gender have also been published.¹⁴ Echoing our findings, lesser work impairment was noted as a correlate of medication adherence by Kutzelnigg *et al.*³⁴ but the same study also observed a negative association of adherence with duration of in-patient care. However, the authors have mentioned that their sample could have been biased as they only included patients stabilized on olanzapine. Higher duration of in-patient stay offers more opportunities for psychoeducation and clarification of medication related risk-benefit tradeoff. This may ex-

Table 3. Summary of logistic regression model for predictors of medication adherence

Variable	Exp (B)	95% CI for B	p value
Occupation	2.780	1.019-7.585	0.046*
Number of depressive episodes	0.216	0.039-1.190	0.078
Number of days spent in hospital	1.020	1.003-1.037	0.021*
Drug Attitude Inventory scores	1.227	1.000-1.506	0.050

CI, confidence interval.

*Significant at $p < 0.05$.

plain our findings.

Positive attitudes towards medications have been robustly linked to medication adherence earlier and our study adds to these findings.^{35,36)} It may be argued that better attitudes could be an epiphenomenon of increased hospital stay but our multivariate analysis showed that positive attitudes towards medication can predict medication adherence even after controlling for hospital stay. Substance use has been shown to influence medication adherence in BD and also play a key role in the relationship between drug attitudes and medication adherence.³⁷⁻³⁹⁾ However, only a very small percentage of our sample had current substance use disorder (SUD; 11.2%) and this may be the reason for non-significant role of substance use in our sample. Nevertheless, many BD patients, irrespective of SUD, deny any illness and disagree with doctors about need for medications.^{40,41)} This means that non-adherence is a serious challenge even in the absence of SUD. We also found that patients with negative drug attitudes at baseline may represent a subgroup at high risk for medication non-adherence and poor outcomes. This has obvious implications from a management perspective. Proper psychoeducation about the benefits of psychotropic medications may address denial of illness. Further, involvement of community health care facilities may surmount lack of access to continued treatment facilities which has been noted to be a reason for non-adherence among Indian patients with schizophrenia⁴²⁾ and may also be relevant to BD.

The major limitations of the study include its cross-sectional design and lack of objective measures to measure medication adherence such as pill count or blood level estimation. Moreover, the entire sample was drawn from a single tertiary care hospital and the results may not necessarily generalize to other settings. Pill counts could not be done as most patients do not come to the follow up clinic with pill boxes or medicine strips unless informed beforehand and this being a cross-sectional study, there was no scope for repeated evaluations. Another limitation is that we have not assessed difference in adherence rates between various mood stabilizers and antipsychotics (first generation vs second generation) separately. We did not contact patients who may have dropped out of the clinic prior to enrollment period of study as we did not have their contact details. The major strength of the study was the use of a validated self-report measure in the local lan-

guage to assess medication adherence patterns. To reduce degree of diagnostic imprecision, we also used the MINI instrument to confirm the lifetime diagnosis of BD. Further, the study had a naturalistic design and therefore, the findings are likely to reflect real world practice.

To conclude, majority of stable and remitted bipolar subjects are poorly adherent with their drug treatment regimens. Those who are employed and those who have spent a higher duration as an in-patient are more likely to be medication adherent as are those who have better drug attitudes and experienced fewer lifetime depressive episodes. Other socio-demographic and illness variables appear to be less helpful in determining medication adherence. Clinicians should focus on providing targeted psychoeducation about illness and more specifically, medication related benefits to BD subgroups such as those with poor attitudes to improve adherence. Other BD subgroups at potential risk of non-adherence such as those with substance abuse and personality disorders need further evaluation. The role of technology in improving medication adherence also warrants evaluation in BD given that simple, low cost mobile health initiatives such as text messages have been found to be beneficial in improving medication adherence in a wide range of conditions including mental health disorders.⁴³⁻⁴⁵⁾

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