

Self-reported medication adherence and its correlates in a lithium-maintained cohort with bipolar disorder at a tertiary care centre in India



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ABSTRACT

Background: Lithium remains a cornerstone of prophylaxis in bipolar disorder (BD), but adherence continues to be a major clinical challenge and merits a closer attention. There is scant literature available in Indian as well as Asian context.

Methods: This study was conducted at Department of Psychiatry, AIIMS, New Delhi with an aim to assess the self-reported medication adherence and its correlates among a naturalistic, lithium-maintained cohort (n = 76) with bipolar disorder. Subjects were included if they were on lithium therapy ≥ 1 year, met DSM-5 diagnosis of bipolar disorder and were in clinical remission (≥ 1 month). Besides sociodemographic and clinical performance, participants were assessed on medication adherence rating scale (MARS), lithium questionnaire for knowledge and lithium attitude questionnaire (LAQ).

Results: Mean age was 35.7 ± 10.6 years (males: 59.2%); median duration of illness and lithium therapy was 84 months and 24.5 months, respectively. Mean MARS score was 6.95 ± 2.81 . Regression analysis (with MARS total as dependent variable) found LAQ score to be the single most significant predictor variable ($\beta = -0.681$, $p < 0.0001$), explaining over 75% of the total variance. In regression model with MARS factor-1 score as dependent variable, the 'LAQ score' ($\beta = -0.601$, $p < 0.0001$) and 'being accompanied by family during psychiatric visits (always/mostly) in the past year' ($\beta = 0.193$, $p = 0.010$) emerged as significant predictor variables.

Conclusion: Adherence in lithium-maintained treatment-seeking cohort of patients with BD remains far from ideal as observed in this naturalistic setting. Lithium-related attitudes and being accompanied by family during psychiatric visits were found to be significant predictors for adherence.

1. Introduction

Bipolar disorder (BD) is a recurrent, episodic mood disorder affecting at least 1% of general population, leading to significant morbidity and disability (Merikangas et al., 2011). The relapses and associated complications such as suicidal attempts and completed suicides are potentially preventable to a large degree with adequate, long-term prophylaxis (Geddes et al., 2013). However, only 20%–60% of patients with BD are adherent to medication (Bates et al., 2010; Greene et al., 2018; Scott and Pope, 2002). Non-adherence contributes at least partly to poorer long-term outcomes in BD, with more relapses, hospitalizations, suicidality and medical expenditures (Belzeaux et al., 2013; Gonzalez-Pinto et al., 2006; Hong et al., 2011).

Lithium remains a cornerstone of prophylaxis in BD, despite of advent of newer agents and is especially indicated for certain subgroups of

patients such as those with positive family history or higher suicidality (Severus et al., 2018; Yatham et al., 2013). Lithium when used prophylactically prevents recurrences, has anti-suicidal properties and some neuroprotective benefits over long term use (Baldessarini et al., 2003; Geddes and Miklowitz, 2013; Won and Kim, 2017). A recent study by Öhlund et al. (2018) found that 54% of lithium-treated patients with BD discontinued lithium, which was much higher than that reported in most effectiveness trials (wherein over a six-month trial, 30% missed doses was reported by less than 5% of subjects) (Sylvia et al., 2014). Thus, it is important to assess the factors associated with medication adherence in order to better understand and design interventions targeting modifiable factors associated with non-adherence.

The bulk of literature available from western developed countries reporting potential factors associated with non-adherence in patients with BD include age, education, polypharmacy, real or perceived side-

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effects, severity of depressive episodes, duration of illness, length of treatment, degree of contact with treatment providers, among others. (Barraco et al., 2012; Johnson et al., 2007; Levin et al., 2016; Lingam and Scott, 2002). There was a paucity of studies specifically focusing on lithium non-adherence, with even fewer of them examining its relation to lithium related knowledge and attitudes held by patients with BD (Dharmendra and Eagles, 2003; de Souza et al., 2013; Rosa et al., 2007; Schumann et al., 1999). A six-year naturalistic follow-up of patients on lithium found that non-adherent patients (constituting 53% of sample) showed significantly more denial of the 'prophylaxis in general', 'effectiveness of lithium' and 'severity of their illness', as assessed by Lithium Attitudes Questionnaire (Schumann et al., 1999). The limited evidence available from these studies suggested that lithium-related attitudes and knowledge might significantly affect medication adherence in lithium-maintained patients with BD.

However, limited literature exists for medication adherence and/or its correlates in lithium-maintained patients from Asian countries (Lee et al., 2019; Moon et al., 2012). Coming to Indian literature; a PubMed based electronic search supplemented with MedInd, Google Scholar and cross-reference search from relevant review papers in Indian context (Avasthi, 2010; Shah et al., 2017), found only a few studies on medication adherence and/or its correlates in BD (Selvakumar et al., 2018; Subramanian et al., 2016; Grover et al., 2014). Of these, the study by Grover et al (2014), which specifically focused on a sample patients maintained on lithium therapy (n = 100), found that nearly one third experience sexual dysfunction and it was associated with poor medication adherence as assessed by brief medication adherence scale. Further, some other Indian studies have also examined adherence among patients with various other psychiatric disorders, for instance, in major depression (Chakraborty et al., 2009), or in general psychiatric out-patients (Sharma et al., 2012).

The present study was planned to assess the medication adherence and explore its correlates, including lithium related knowledge and attitudes, among a clinical sample of euthymic patients with BD on lithium prophylaxis at a tertiary care centre in India.

2. Materials and methods

This observational, cross-sectional study was conducted at the outpatient clinic, Department of Psychiatry, A.I.I.M.S., New Delhi during the period from April 2018 to January 2019. Ethical clearance was obtained from the Institutional Ethics Committee.

2.1. Selection criteria

A purposive treatment-seeking sample of out-patients was recruited for the study after obtaining their informed written consent. The patients with either gender, aged 18 years or above, diagnosed with BD as per DSM-5 criteria (American Psychiatric Association, 2013), being prescribed lithium-maintenance therapy for at least one year or more, and in clinical remission for at least one month or more (as per clinical history and treatment records) at the time of assessment, and scoring below standard cut-offs on Hamilton rating scale for depression (HAM-D < 7) and Young mania rating scale (YMRS < 4) were considered for inclusion in the study. The exclusion criteria included a comorbid diagnosis of any major psychiatric disorder except tobacco or alcohol dependence, intellectual disability, and refusal to provide consent. The clinical care of the patients continued as usual by their treating psychiatrists, and no modification/change was done as a result of their participation in this study. The prescription of psychotropics or medications other than lithium was not an exclusion criterion. Similarly, comorbid medical/physical diseases were not a criterion for exclusion provided it did not interfere with study assessments or participation.

2.2. Assessment tools

Patients were assessed using the following instruments:

- **Medication adherence rating scale (MARS):** It is a widely used, valid and reliable instrument to measure the degree of adherence to psychotropic medications (Thompson et al., 2000). Originally developed from Drug Attitude Inventory (Hogan et al., 1983), with an aim to refine and overcome its limitations, MARS was observed to have a greater validity and higher clinical utility. It is a brief scale with 10 items, including reverse items, which relate to adherence while also recognizing the complexity of behavior. Patients who are otherwise adherent and sometimes forget to take medication doses fare better compared to those who actively interrupt medication or stop it after perceiving improvement. Overall, higher MARS total scores are indicative of better adherence, and has been widely used as a measure of adherence in clinical research.
- The exploratory factor analysis of MARS originally yielded a three-factor structure (Thompson et al., 2000), which was subsequently confirmed in a larger sample of patients (Fialko et al., 2008), reflecting the multi-dimensional nature of adherence assessed by this instrument. Factor 1 (items 1–4) accounted for the maximum variance and represents 'medication adherence behavior'; while factor 2 (items 5–8) and factor 3 (items 9–10) represent subjects' "attitude to taking medication" and "negative side effects and attitudes" respectively. It has also been suggested that the factor 1 sub-score might be a more preferable, and even a better measure of adherence behavior than MARS total score (Fialko et al., 2008). Further, this 4-item factor 1 scores had been demonstrated to correspond better with the Morisky adherence scale scores (Morisky et al., 1986). Thus, a few prior studies have used these factor or dimension sub-scores in addition to MARS total score for examining adherence (Belzeaux et al., 2013).
- **Lithium questionnaire (LQ) for knowledge:** It is a semi-structured questionnaire developed and used previously in a study by Sing Lee et al (1992), with 13 yes/no items assessing subjects' knowledge about lithium, and an empty space provided next to some items to seek elaboration from the respondent, as required. The theme of questions included awareness of name and purpose of medication, adverse effects, toxicity signs, blood tests, dietary or other precautions. The higher scores on LQ suggests better lithium related knowledge.
- **Lithium attitude questionnaire (LAQ):** It consists of 19 items for rating of individual attitudes towards prophylactic lithium treatment (Harvey, 1991). Each item is in a Yes/No format, with replies alternating between affirmation and denial, to obviate the effect of response set bias. LAQ has a possible score range of 0–19, with higher scores indicating greater negative attitudes and lower scores indicating positive attitudes. The LAQ was found to be the only valid and reliable tool for assessing attitudes toward lithium.

2.3. Study procedure

All patients presenting to the outpatient department with an assigned diagnosis of BD were approached for inclusion in this study. The diagnosis of BD was ascertained as per DSM-5 by a trained psychiatrist (study investigators), and patients were included if inclusion and exclusion criteria were fulfilled. The participants were assessed using the socio-demographic sheet and a semi-structured clinical performa designed for the purpose of present study. The study instruments viz. MARS, LQ, and LAQ were administered by the researchers. Assessments were carried out in a single session lasting for about an hour. A written informed consent was taken from all the participants.

2.4. Statistical analysis

Statistical analysis was carried out using SPSS version 23.0 (Armonk, NY, IBM Corp). Descriptive statistics were used to tabulate socio-demographic and clinical variables. Means and standard deviations were used for continuous variables, whereas frequencies and percentages were used for categorical variables. The distribution of study variables was checked by using normality plots and Kolmogorov–Smirnov test, which revealed a non-normal distribution for the data.

The bivariate analysis for assessing relationship of medication adherence (as measured by MARS total score and factor 1 sub-score) to various study variables/factors (socio-demographic and clinical characteristics, lithium related knowledge, and attitudes) was examined using non-parametric tests of Spearman's correlation for continuous variables and Mann-Whitney U test for categorical variables. A two-tailed p-value of < 0.05 was considered significant for bivariate analyses.

Multivariate analyses were performed by conducting multiple linear regression using simultaneous model to determine significant predictors of medication adherence. The selection of simultaneous model during linear regression allowed for reduction in the inflation of type 1 error rate. The dependent variable was MARS total score and MARS factor-1 (medication adherence behaviour) sub-score. The independent variables entered in the model included factors having significant association ($p < 0.05$) with adherence in the bivariate analysis. To check for multicollinearity, the tolerance and variance inflation factor values were examined, which did not reveal significant multicollinearity. The recommended maximum value of 10 for variation inflation factor and a minimum value of 0.1 for tolerance statistic were used as cut-offs for acceptable level of multicollinearity. The final model incorporated the standardized β coefficients, which represent a change in the standard deviation of the dependent variable (MARS) resulting from a change of one standard deviation in the various independent variables. The independent variables with higher standardized beta coefficients have a greater relative effect on adherence.

To control for possible inflation of Type I error rate due to the generation of two linear regression models for adherence, we applied a Bonferroni correction and considered a result significant only if p-value was < 0.025 (i.e. 0.05/2) for multivariate analyses. Missing value imputation was not done.

3. Results

A total of 84 patients with BD fulfilling the selection criteria were recruited, of which eight had to be excluded from analysis due to missing/incomplete data pertaining to adherence and/or related study variables. The final study sample comprised of 76 participants.

3.1. Socio-demographic and clinical characteristics

Table 1 describes the detailed socio-demographic and clinical characteristics of study participants. The mean age of study sample was 35.7 ± 10.6 years (range: 18.5–63 years), with a majority of participants being males (59.2%). Almost all the participants had received some form of formal education (93.4%), with 35.5% ($n = 27$) of them having a graduate degree or above. The median duration of illness was 84 months (inter-quartile range IQR: 44.0–189.0), and median duration of lithium treatment was 24.5 months (IQR: 15.0–64.5). The median number of visits to a psychiatrist in past year was 4.00 (IQR: 2.2–5.0).

3.2. Medication adherence

The mean score on MARS was 6.95 ± 2.81 (with max possible score: 10). Table 2 shows the item-wise frequency of responses on MARS. Fig. 1 shows the distribution of MARS scores in the study

Table 1
Socio-demographic and clinical characteristics of study sample (N = 76).

Variable	Mean \pm SD or Frequency (%)
Age (in years)	35.7 \pm 10.6
Gender:	45 (59.2%)
Male	31 (40.8%)
Female	
Education [#] :	44 (57.9%)
Education up to 12th standard	27 (35.5%)
Graduate or above	
Marital status:	27 (35.5%)
Never married	44 (57.9%)
Married	5 (6.6%)
Separated/divorced	
Socioeconomic status (SES)	7 (9.2%)
Lower	38 (50.0%)
Lower middle	29 (38.2%)
Upper Middle	2 (2.6%)
Upper	
Duration of illness (in months)	124.1 \pm 97.0
Duration of lithium therapy (in months)	50.1 \pm 59.1
Number of visits with psychiatrist in past year	4.4 \pm 3.4
Being accompanied by family in psychiatric visits in past year ^c :	26 (35.6%)
Never/sometimes	47 (64.4%)
Mostly/always	
Number of serum lithium estimations in past year ^b	2.6 \pm 1.8
Frequency of lithium intake/day:	6 (7.9%)
Once	70 (92.1%)
Twice or thrice	
Lithium monotherapy as prophylaxis ^a :	37 (49.3%)
Yes	38 (50.7%)
No	
Lithium prescription in first degree relative ^a :	6 (8.0%)
Yes	69 (92.0%)
No	
Prior psychiatric hospitalization:	41 (53.9%)
Yes	35 (46.1%)
No	
Prior electro-convulsive treatment:	7 (9.2%)
Yes	69 (90.8%)
No	
Comorbid alcohol dependence:	5 (6.6%)
Yes	71 (93.4%)
No	
Comorbid hypertension ^a :	5 (6.7%)
Yes	70 (93.3%)
No	
Comorbid diabetes ^b :	5 (6.8%)
Yes	69 (93.2%)
No	
Comorbid hypothyroidism ^a :	5 (6.7%)
Yes	70 (93.3%)
No	
Lithium questionnaire (LQ) for knowledge	6.7 \pm 3.1
Lithium attitude questionnaire (LAQ) score	7.8 \pm 2.8
Medication adherence rating scale (MARS) total score	6.9 \pm 2.8

[#] Five (6.6%) participants were either illiterate or not formally educated.

^a Missing data for one participant.

^b Missing data for two participants.

^c Missing data for three participants. SD Standard deviation.

sample. The MARS total score of ≤ 7 was found in 54.7% of study sample.

3.3. Bivariate analyses

Table 3 shows the relationship of medication adherence to various study variables. The MARS total score was significantly associated with following nine variables: being married ($p = 0.017$), number of visits to psychiatrist in past year ($p < 0.0001$), being accompanied by family

Table 2
Pattern of non-adherence: item-wise responses on Medication adherence rating scale (MARS) (n = 76).

MARS question	Affirmative response	
	n	%age
1 Do you ever forget to take your medication?	48	63.2 %
2 Are you careless at time about taking your medication?	60	78.9 %
3 When you feel better, do you sometimes stop taking medication?	52	68.4 %
4 Sometimes if you feel worse when you take the medication, do you stop taking it?	48	63.2 %
5 I take medication only when I am sick.	64	84.2 %
6 It is unnatural for my mind and body to be controlled by medication.	37	48.7 %
7 My thoughts are clear on medication.	44	57.9 %
8 By staying on medication, I can prevent getting sick.	67	88.2 %
9 I feel weird, like a “zombie” on medication.	65	85.5 %
10 Medication makes me feel tired and sluggish.	43	56.6 %

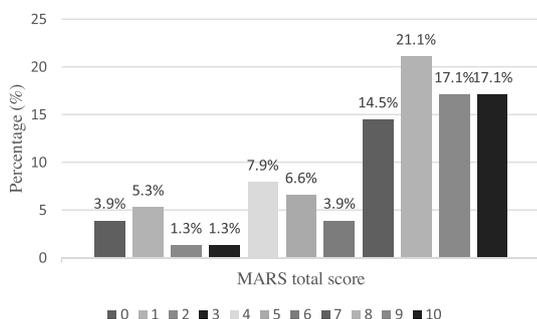


Fig. 1. Medication adherence rating scale: score distribution (MARS total score 1–10).

members (mostly/always) for psychiatric visits in past year ($p = 0.005$), number of serum lithium estimations in past year ($p = 0.024$), frequency of lithium dosage per day ($p = 0.004$), comorbid alcohol dependence ($p = 0.01$), comorbid hypothyroidism ($p = 0.030$), lithium related knowledge ($p < 0.0001$) and LAQ score ($p < 0.0001$).

A similar bivariate analysis was repeated for MARS factor 1 sub-score which revealed the same significant associations as described above (results not shown).

3.4. Multivariate analyses

Multivariate analyses were performed, as described previously in the statistical analysis, by conducting multiple linear regression using simultaneous model to determine significant predictors of medication adherence. After correction for multiple testing, a p -value of < 0.025 was deemed to be significant.

As shown in Table 4, the lithium-related attitude (LAQ total score) was a significant predictor of medication adherence (as assessed by both MARS total score and factor 1 sub-score). Further, being accompanied by family member (always/mostly) for psychiatric visits in past year was a significant predictor of MARS factor 1 sub-score but not MARS total score (Table 4). The regression models were able to explain 75.7% and 72.1% of the total variance observed in MARS total score and its factor 1 sub-score respectively.

4. Discussion

This is one of the few studies from India to report on predictors of non-adherence in BD and reports from an exclusive sample of lithium-

Table 3
Sociodemographic and clinical correlates of medication adherence (MARS total) in lithium-maintained subjects with bipolar disorder (N = 76).

Variable	Spearman's correlation coefficient or MARS total mean \pm SD	p value (Spearman correlation or Mann-Whitney U test)
Age (in years)	−0.20	0.083
Gender:	6.6 \pm 2.9	0.369
Male	7.3 \pm 2.5	
Female		
Education:	6.8 \pm 2.8	0.767
Education up to 12th standard	7.1 \pm 2.8	
Graduate or above		
Marital status:	6.3 \pm 2.9	0.017 *
Married	7.7 \pm 2.4	
Never married/separated/divorced		
Socioeconomic status [#]	0.376	0.95
Lower		
Lower middle		
Upper middle		
Upper		
Duration of illness (in months)	−0.18	0.102
Duration of lithium therapy (in months)	−0.04	0.677
Number of visits to a psychiatrist in past year	0.47	< 0.0001*
Being accompanied by family in psychiatric visits in past year ^c :	5.5 \pm 3.3	0.005 *
Never/sometimes	7.7 \pm 2.1	
Mostly/always		
Number of serum lithium estimations in past year ^b	0.26	0.024 *
Frequency of lithium intake/day:	9.5 \pm 0.8	0.004 *
Once	6.7 \pm 2.8	
Twice or thrice		
Lithium polytherapy as prophylaxis ^a :	6.8 \pm 2.4	0.368
Yes	7.0 \pm 3.1	
No		
Lithium prescription in first degree relative ^a :	7.8 \pm 0.9	0.797
Yes	6.8 \pm 2.9	
No		
Prior psychiatric hospitalization:	6.4 \pm 3.2	0.396
Yes	7.4 \pm 2.0	
No		
Prior electro-convulsive treatment:	5.7 \pm 3.0	0.241
Yes	7.0 \pm 2.7	
No		
Comorbid alcohol dependence:	2.8 \pm 2.1	0.001 *
Yes	7.2 \pm 2.6	
No		
Comorbid hypertension ^a :	5.2 \pm 4.0	0.355
Yes	7.0 \pm 2.7	
No		
Comorbid diabetes ^b :	5.8 \pm 3.7	0.437
Yes	7.1 \pm 2.6	
No		
Comorbid hypothyroidism ^a :	9.2 \pm 1.0	0.030 *
Yes	6.7 \pm 2.8	
No		
Lithium questionnaire (LQ) for knowledge	0.47	< 0.0001*
Lithium attitude questionnaire (LAQ) score	−0.73	< 0.0001*

Statistical analysis by Spearman correlation or Mann-Whitney U test or #Kruskal Wallis test; SD Standard deviation, MARS Medication adherence rating scale.

^a Missing data for one participant.

^b Missing data for two participants.

^c Missing data for three participants.

maintained patients, adding to the very few studies available on adherence in BD from the Indian/Asian context. The study sample comprised of a homogeneous group of euthymic out-patients with BD (of 1.5–33 years duration) on lithium maintenance therapy (for 1 to 15 years), and were in follow-up in a naturalistic setting. Further, the study sample had an adequate representation from either gender and diverse age range (18–63 years).

Lithium is a peculiar drug in several respects and is known to be effective only at doses which maintain its serum level above a particular threshold (therapeutic window: 0.6–1.2 mmol/L). Even a slight dose reduction (by half or one tablet) or skipping a few doses has the potential to precipitate another mood episode by reducing the serum lithium levels. Further, an abrupt drug discontinuation in the context of lithium therapy can possibly lead to a worsened course of BD, including a risk of developing rapid cycling affective disorder. Baldessarini et al (1999) found that rapid discontinuation of lithium produced more episode recurrences compared to a gradual taper, which is an area of potential concern for lithium-maintained patients who intermittently and abruptly stop their medication. An optimal level of adherence to lithium therapy is an important step towards ensuring its effectiveness in prevention of mood episodes. Nonetheless, it continues to be a significant clinical challenge in actual practice and merits a closer attention.

The present study reveals a sub-optimal adherence level in study participants with an average MARS score of 6.95 ± 2.81 (with maximum possible score of 10), reflecting a scope to enhance adherence even among euthymic BD sample of patients seeking routine treatment at psychiatry outpatient clinic. Further, about half of the study participants (54.7%) reported low medication adherence (when defined using MARS total score of ≤ 7). This is comparable to the finding from only other Indian study conducted among patients with BD on treatment with various mood stabilizers including lithium (Selvakumar et al., 2018), which reported a majority (60.6%) of patients to had a low adherence to their prescribed treatment regimens.

Medication adherence is admittedly a complex behaviour influenced by a host of patient-related (e.g. age, gender or attitudes etc.), illness-related (e.g. duration or prior hospitalization etc.), other clinical (e.g. comorbid substance use or family history) and medication related (e.g. type, dose regimen etc.) factors, besides clinician or service-delivery related factors (Busby and Sajatovic, 2010). The present study did not focus on clinician-related or service delivery factors, but attempted to assess several of the above-mentioned patient-related, illness-related and treatment-related factors in relation to adherence in lithium-maintained patients with BD.

Several important factors associated with medication adherence emerged from bivariate analysis, including marital status ($p = 0.017$), number of visits to psychiatrist in past year ($p < 0.0001$), being

accompanied by family members (mostly/always) for psychiatric visits in past year ($p = 0.005$), number of serum lithium estimations in past year ($p = 0.024$), frequency of lithium dosage per day ($p = 0.004$), comorbid alcohol dependence ($p = 0.01$), comorbid hypothyroidism ($p = 0.030$), lithium related knowledge ($p < 0.0001$) and LAQ score ($p < 0.0001$). These findings from lithium-maintained patients are broadly in consonance with the available literature on treatment adherence in BD in general, with some important differences (e.g. no relationship to duration of illness or duration of treatment). In existing literature, factors associated with non-adherence in BD patients include a younger age, low education status, fewer out-patient visits, early course (1st year of illness), a longer duration of treatment, denial of illness, real or perceived side-effects, polypharmacy, lack of information, negative attitudes, lack of social support or substance use (Bates et al., 2010; Busby and Sajatovic, 2010; Clatworth et al., 2007; Col et al., 2014; Leclerc et al., 2013; Sajatovic et al., 2015).

The present study did not find a relationship of adherence with age, education level or gender in this sample of lithium-maintained patients with BD. This is in line with the mixed findings reported in some of the previous studies. Age (< 40 years) and marital status (being unmarried/single) have been reported to influence adherence in some of the available studies (Levin et al., 2016; Pompili et al., 2013), though not in all studies (Belzeaux et al., 2013). In present study, married marital status was negatively related to adherence in bivariate analysis. We cannot speculate much on the underlying reasons for this observed association between non-adherence and married status, however a previous study on lithium sample by Grover et al (2014) found that sexual dysfunction among patients on lithium was more likely to be associated with non-adherence. Similarly, gender has an inconsistent relationship to adherence in the available literature (Sajatovic et al., 2011). Substance abuse or disorder has also been linked to poor compliance (Montes et al., 2013; Perlis et al., 2010), though in present study, the comorbid substance use disorder was not a significant predictor of adherence in regression analyses. The relatively small number of patients with history of substance use disorder in the current study might have led to an underestimation of the association.

On regression analysis, the lithium related attitude (assessed using LAQ score) was found to be the single most important predictor of medication adherence (MARS total) in lithium-maintained patients with BD, explaining over 75% of the total observed variance. The attitude themes covered by LAQ include resistance to prophylaxis in general, denial of therapeutic effectiveness of lithium, fear of side effects, difficulties with daily routine of medication intake, denial of severity of illness, negative attitudes toward drugs in general and lack of information about lithium, all of which are potentially important for maintaining long-term adherence. This is in line with findings of previous studies, with more positive attitudes (as measured by LAQ score

Table 4

Predictors of adherence according to regression analysis (using MARS total score and MARS factor 1 score as dependent variables).

Independent variables	MARS total score [#]				MARS (factor 1) sub-score ^{##}			
	β	SE	95% CI for B	p	β	SE	95% CI for B	p
Being married	-0.122	0.372	-1.435 to 0.052	0.068	0.126	0.201	-0.762 to 0.041	0.077
Number of visits to a psychiatrist (last year)	0.141	0.060	-0.005 to 0.233	0.061	0.135	0.032	-0.010 to 0.119	0.093
Number of serum lithium estimations (last year)	-0.006	0.111	-0.231 to 0.211	0.930	0.036	0.060	-0.091 to 0.148	0.639
Being accompanied by family in psychiatric visits (always/ mostly)	0.119	0.398	-0.100 to 1.492	0.085	0.193	0.215	0.138 to 0.998	0.010 *
Once a day lithium dosing	0.092	0.685	-0.436 to 2.304	0.178	0.101	0.370	-0.224 to 1.255	0.169
Comorbid alcohol dependence	-0.039	0.787	-2.006 to 1.140	0.584	0.001	0.425	-0.858 to 0.842	0.985
Comorbid hypothyroidism	0.090	0.736	-0.476 to 2.466	0.181	0.091	0.397	-0.290 to 1.300	0.209
Lithium questionnaire (LQ) score for knowledge	0.032	0.073	-0.116 to 0.176	0.684	0.072	0.039	-0.045 to 0.113	0.397
Lithium attitude questionnaire (LAQ) score	-0.681	0.049	-0.506 to -0.312	< 0.0001 *	0.601	0.026	-0.234 to -0.129	< 0.0001 *

β Standardized beta coefficient; SE Standard error; CI Confidence interval; B Unstandardized beta coefficients.

* p-value < 0.025 considered significant after multiple testing.

[#] Model-1 $R^2 = 0.757$ ($F = 21.493$; $p < 0.0001$).

^{##} Model-2 $R^2 = 0.721$ ($F = 17.823$; $p < 0.0001$).

or drug attitude inventory or similar Likert scale responses) being associated with a greater likelihood of continuing lithium intake in patients with BD (Arvilommi et al., 2014; Dharmendra and Eagles, 2003; Ghaffari-Nejad et al., 2015). Further, certain specific negative attitude themes associated with poor adherence include, a fear of dependence, shame, considering medication intake to be unnatural or unhealthy, discomfort with having one's mood controlled by medication, an unwillingness to take medication, and low self-efficacy for medication-taking behaviour (Levin et al., 2016). In the previous Indian study by Selvakumar et al. (2018) on factors associated with adherence in BD, 'being employed' and 'having spent a greater number of days in hospital' had emerged as significant predictors, while another Indian work found that non-adherence was associated with greater subsyndromal manic symptoms and a shorter duration of illness (Subramanian et al., 2016).

While lithium-related attitudes had been consistently found to be related to adherence, lithium related knowledge was not found to impact adherence in the present study. This has also been reflected in the equivocal findings of previous studies on the association between lithium related knowledge and medication adherence (Rosa et al., 2007; Sing Lee et al., 1992). This suggests that a better lithium related knowledge does not necessarily translate directly into positive changes in medication adherence behaviour, though it may be helpful in increasing medication adherence by its indirect effects on other related factors such as by promoting a more positive lithium treatment related attitudes.

In the regression model using MARS-factor 1 sub-score as the dependent variable, the lithium related attitude (LAQ score) was still found to be a significant predictor of adherence. In addition, being accompanied by a family member (defined as first degree relative or spouse) always/mostly during psychiatric visits in past year also emerged as another significant predictor of adherence behaviour. The active involvement of close family members (spouse or first-degree relatives) in treatment process is likely to improve adherence in severe mental illnesses like BD. Findings from previous studies support the efficacy of family-focused interventions in increasing medication adherence among patients with BD (Miklowitz et al., 2003; Pakpour et al., 2017; Scott et al., 2012). The positive role played by family members in caring for mentally ill in Indian context has been well acknowledged, with literature pointing to multiple roles played by family members, such as supervision of medications, taking the patient to a psychiatrist, taking care of day-to-day activities, looking after financial needs, among others (Avasthi, 2010; Chadda, 2014). People from eastern cultures, such as in the Middle East, India, or China traditionally report collectivistic value orientations (Tse and Ng, 2014) wherein patients are often supported and cared by their family, which act as an important source of social support. Therefore, suitable adaptation of mental health recovery frameworks to suit cultural context that adequately engages both service users as well as their families is recommended (Dirik et al., 2017).

While majority of studies have used MARS total score as a sole factor to represent medication adherence, some studies have used its factor or dimension scores individually in addition to the total score (Belzeaux et al., 2013). While factor 2 and 3 largely represent attitude dimension, the factor 1 sub-score (items 1–4) represents medication adherence behavior. Therefore, MARS factor 1 subscore has been suggested to be a more preferable measure of adherence (Fialko et al., 2008), and had also been demonstrated to correspond better with the Morisky adherence scale (Morisky et al., 1986). Thus, in view of this, we have used the factor 1 sub-score in addition to the MARS total score, as a more specific measure of adherence behavior.

The findings from present study emphasize that it is important to focus on negative attitudes towards lithium treatment in order to improve adherence. The clinical implications of this include a need to address non-adherence and related factors by means of appropriate evidence-based interventions aimed at making attitudinal shifts in patients with BD and enhancing medication adherence. The use of

motivational interviewing, medication routines, enhanced contact with treatment providers and cognitive behavioural strategies might also be effective, though no single intervention reportedly had unquestionable efficacy.

The strengths of present study include application of rigorous, predefined selection criteria, including a cut-off of ≥ 1 year of prescribed lithium therapy and use of valid and reliable scales for adherence and attitudes to facilitate comparison with prior literature. The study findings must, however, be interpreted in context of certain limitations which include a relatively small sample size, purposive sample from a tertiary care centre, use of self-reported measure of adherence, possibility of residual/subsyndromal mood symptoms in sample and non-generalizability to those on lithium for less than a year. Further, the study did not include an exhaustive set of potential patient-related, socio-cultural or service delivery related factors, facilitators or barriers which might have impacted the adherence.

The present study was conceived as part of needs assessment as an initial part of quality improvement, however further studies are required to develop evidence-based initiatives to improve the degree of adherence among patients in contact with out-patient treatment services. Priorities for future research in this direction include longitudinal studies on medication adherence and inclusion of multiple methods, including objective measures, to assess adherence. We also wish to highlight that the service delivery aspects for patients on regular lithium therapies remain understudied in Indian context and needs to be brought into focus in future studies. Quality improvement initiatives are needed for patients on prescribed long-term lithium therapy.

World-wide, there is a decline in the use of lithium in spite of a robust scientific evidence favoring its use in BD with several advantages, including anti-suicidal properties. This downward trend is often attributed to logistics pertaining to lithium monitoring, safety concerns and a commercial bias against lithium which is non-patented. Akin to clozapine, there is need to perhaps revisit and consider the 'specialized care pathways' for lithium at a wider scale, which can increase the lithium prescriptions and help in ensuring the compliance and safety aspects. (Tibrewal et al., 2019) The role of clinical pharmacy services must also be recognised which can play a positive role in monitoring the adherence among people on long-term therapies which require a close supervision. (Eltorki et al., 2019) The lithium clinics or specialized bipolar clinics with provision of integrated and comprehensive services can immensely contribute to patient adherence, clinical services and related research.

To conclude, adherence in lithium-maintained treatment-seeking cohort of patients with BD remains far from ideal as observed in a naturalistic setting. Lithium-related attitudes and being accompanied by family member during psychiatric visits in past year were found to be significant predictors for medication adherence. Special attention needs to be devoted to develop effective interventions aimed to address the negative attitudes and promote family involvement in the treatment process.

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References

- American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. American Psychiatric Publishing, Arlington, VA.
- Arvilommi, P., Suominen, K., Mantere, O., Leppämaä, S., Valtonen, H., Isometsä, E., 2014. Predictors of adherence to psychopharmacological and psychosocial treatment in bipolar I or II disorders - an 18-month prospective study. *J. Affect. Disord.* 155, 110–117.
- Avasthi, A., 2010. Preserve and strengthen family to promote mental health. *Indian J. Psychiatry* 52, 113–126.
- Baldessarini, R.J., Tondo, L., Hennen, J., 2003. Lithium treatment and suicide risk in major affective disorders: update and new findings. *J. Clin. Psychiatry* 64 (Suppl. S5),

- 44–52.
- Baldessarini, R.J., Tondo, L., Viguera, A.C., 1999. Discontinuing lithium maintenance treatment in bipolar disorders: risks and implications. *Bipolar Disord.* 1 (1), 17–24.
- Barraco, A., Rossi, A., Nicolò, G., Group, E.S., 2012. Description of study population and analysis of factors influencing adherence in the observational Italian study “Evaluation of Pharmacotherapy Adherence in Bipolar Disorder” (EPHAR). *CNS Neurosci. Ther.* 18 (2), 110–118.
- Bates, J.A., Whitehead, R., Bolge, S.C., Kim, E., 2010. Correlates of medication adherence among patients with bipolar disorder: results of the bipolar evaluation of satisfaction and tolerability (BEST) study: a nationwide cross-sectional survey. *Prim. Care Companion J. Clin. Psychiatry* 12 (5) PCC.09m00883.
- Belzeaux, R., Correard, N., Boyer, L., Etain, B., Loftus, J., Bellivier, F., et al., 2013. Depressive residual symptoms are associated with lower adherence to medication in bipolar patients without substance use disorder: results from the FACE-BD cohort. *J. Affect. Disord.* 151, 1009–1015.
- Busby, K.K., Sajatovic, M., 2010. REVIEW: patient, treatment, and systems-level factors in bipolar disorder nonadherence: a summary of the literature. *CNS Neurosci. Ther.* 16 (5), 308–315.
- Chadda, R.K., 2014. Caring for the family caregivers of persons with mental illness. *Indian J. Psychiatry* 56, 221–227.
- Chakraborty, K., Avasthi, A., Kumar, S., Grover, S., 2009. Attitudes and beliefs of patients of first episode depression towards antidepressants and their adherence to treatment. *Soc. Psychiatry Psychiatr. Epidemiol.* 44, 482–488.
- Clatworth, J., Bowskill, R., Rank, T., Parham, R., Horne, R., 2007. Adherence to medication in bipolar disorder: a qualitative study exploring the role of patients’ beliefs about the condition and its treatment. *Bipolar Disord.* 9 (6), 656–664.
- Col, S.E., Caykoylu, A., Karakas Ugurlu, G., Ugurlu, M., 2014. Factors affecting treatment compliance in patients with bipolar I disorder during prophylaxis: a study from Turkey. *Gen. Hosp. Psychiatry* 36 (2), 208–213.
- de Souza, C., Vedana, K.G.G., Mercedes, B.P., do, C., Miaso, A.I., 2013. Bipolar disorder and medication: adherence, patients’ knowledge and serum monitoring of lithium carbonate. *Rev. Lat. Enfermagem* 21, 624–631.
- Dharmendra, M.S., Eagles, J.M., 2003. Factors associated with patients’ knowledge of and attitudes towards treatment with lithium. *J. Affect. Disord.* 75, 29–33.
- Dirik, A., Sandhu, S., Giacco, D., Barrett, K., Bennisson, G., Collinson, S., et al., 2017. Why involve families in acute mental healthcare? A collaborative conceptual review. *BMJ Open* 7, e017680.
- Eltorki, Y., Abdallah, O., Omar, N., Zolezzi, M., 2019. Perceptions and expectations of health care providers towards clinical pharmacy services in a mental health hospital in Qatar. *Asian J. Psychiatr.* 42, 62–66.
- Fialko, L., Garety, P.A., Kuipers, E., Dunn, G., Bebbington, P.E., Fowler, D., Freeman, D., 2008. A large-scale validation study of the Medication Adherence Rating Scale (MARS). *Schizophr. Res.* 100, 53–59.
- Geddes, J.R., Miklowitz, D.J., 2013. Treatment of bipolar disorder. *Lancet* 381 (9878), 1672–1682.
- Ghaffari-Nejad, A., Mashayekhi, A., Mazhari, S., Ghayoumi, A., 2015. Factors associated with drug non-adherence after discharge among patients with mood disorders hospitalized in Shahid Beheshti Hospital in Kerman: a prospective study. *Zahedan J Res Med Sci* 17 (4), e968.
- Gonzalez-Pinto, A., Mosquera, F., Alonso, M., López, P., Ramírez, F., Vieta, E., Baldessarini, R.J., 2006. Suicidal risk in bipolar I disorder patients and adherence to long-term lithium treatment. *Bipolar Disord.* 8 (5 Pt 2), 618–624.
- Greene, M., Paladini, L., Lemmer, T., Piedade, A., Touya, M., Clark, O., 2018. Systematic literature review on patterns of pharmacological treatment and adherence among patients with bipolar disorder type I in the USA. *Neuropsychiatr. Dis. Treat.* 14, 1545–1559.
- Grover, S., Ghosh, A., Sarkar, S., Chakrabarti, S., 2014. Avasthi A. Sexual dysfunction in clinically stable patients with bipolar disorder receiving lithium. *J. Clin. Psychopharmacol.* 34 (August 4), 475–482.
- Harvey, S.N., 1991. The development and descriptive use of the lithium attitudes questionnaire. *J. Affect. Disord.* 22, 209–211.
- Hogan, T.P., Awad, A.G., Eastwood, R., 1983. A self-report scale predictive of drug compliance in schizophrenics: reliability and discriminative validity. *Psychol. Med.* 13, 177–183.
- Hong, J., Reed, C., Novick, D., Haro, J.M., Aguado, J., 2011. Clinical and economic consequences of medication non-adherence in the treatment of patients with a manic/mixed episode of bipolar disorder: results from the European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM) study. *Psychiatry Res.* 30 (190(1)), 110–114.
- Johnson, F.R., Ozdemir, S., Manjunath, R., Hauber, A.B., Burch, S.P., Thompson, T.R., 2007. Factors that affect adherence to bipolar disorder treatments: a stated-preference approach. *Med. Care* 45, 545–552.
- Leclerc, E., Mansur, R.B., Brietzke, E., 2013. Determinants of adherence to treatment in bipolar disorder: a comprehensive review. *J. Affect. Disord.* 149 (1–3), 247–252.
- Lee, Y., Lee, M.S., Jeong, H.G., Youn, H.C., Kim, S.H., 2019. Medication adherence using electronic monitoring in severe psychiatric illness: 4 and 24 weeks after discharge. *Clin. Psychopharmacol. Neurosci.* 17 (2), 288–296.
- Levin, J.B., Krivenko, A., Howland, M., Schlachet, R., Sajatovic, M., 2016. Medication adherence in patients with bipolar disorder: a comprehensive review. *CNS Drugs* 30, 819–835.
- Lingam, R., Scott, J., 2002. Treatment non-adherence in affective disorders. *Acta Psychiatr. Scand.* 105, 164–172.
- Merikangas, K.R., Jin, R., He, J.P., Kessler, R.C., Lee, S., Sampson, N.A., et al., 2011. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. *Arch. Gen. Psychiatry* 68 (3), 241–251.
- Miklowitz, D.J., George, E.L., Richards, J.A., 2003. A randomized study of family-focused psychoeducation and pharmacotherapy in the outpatient management of bipolar disorder. *Arch. Gen. Psychiatry* 60, 904–912.
- Montes, J.M., Maurino, J., de Dios, C., Medina, E., 2013. Suboptimal treatment adherence in bipolar disorder: impact on clinical outcomes and functioning. *Patient Pref Adherence* s, 89–94.
- Moon, E., Chang, J.S., Kim, M.Y., Seo, M.H., Cha, B., Ha, T.H., Choi, S., Cho, H.S., Park, T., Ha, K., 2012. Dropout rate and associated factors in patients with bipolar disorders. *J. Affect. Disord.* 141 (1), 47–54.
- Morisky, D.E., Green, L.W., Levine, D.M., 1986. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med. Care* 24, 67–74.
- Öhlund, L., Ott, M., Oja, S., Bergqvist, M., Lundqvist, R., Sandlund, M., Salander, Renberg, E., Werneke, U., 2018. Reasons for lithium discontinuation in men and women with bipolar disorder: a retrospective cohort study. *BMC Psychiatry* 18 (1), 37.
- Pakpour, A.H., Modabbernia, A., Lin, C.Y., 2017. Promoting medication adherence among patients with bipolar disorder: a multicenter randomized controlled trial of a multifaceted intervention. *Psychol. Med.* 47, 2528–2539.
- Perlis, R.H., Ostacher, M.J., Miklowitz, D.J., Hay, A., Nierenberg, A.A., Thase, M.E., Sachs, G.S., 2010. Clinical features associated with poor pharmacologic adherence in bipolar disorder: results from the STEP-BD study. *J. Clin. Psychiatry* 71, 296–303.
- Pompili, M., Venturini, P., Palermo, M., Stefani, H., Seretti, M.E., Lamis, D.A., et al., 2013. Mood disorders medications: predictors of nonadherence—review of the current literature. *Expert Rev. Neurother.* 13 (7), 809–825.
- Rosa, A.R., Marco, M., Fachel, J.M., Kapczinski, F., Stein, A.T., Barros, H.M., 2007. Correlation between drug treatment adherence and lithium treatment attitudes and knowledge by bipolar patients. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 31 (1), 217–224.
- Severus, E., Bauer, M., Geddes, J., 2018. Efficacy and Effectiveness of Lithium in the Long-Term Treatment of Bipolar Disorders: An Update 2018. *Pharmacopsychiatry* 51 (5), 173–176.
- Shah, N., Grover, S., Rao, G.P., 2017. Clinical practice guidelines for management of bipolar disorder. *Indian J. Psychiatry (Suppl 1)*, S51–S66.
- Sajatovic, M., Levin, J.B., Sams, J., 2015. Symptom severity, self-reported adherence, and electronic pill monitoring in poorly adherent patients with bipolar disorder. *Bipolar Disord.* 17 (6), 653–661.
- Sajatovic, M., Micula-Gondek, W., Tatsuoka, C., Bialko, C., 2011. The relationship of gender and gender identity to treatment adherence among individuals with bipolar disorder. *Gen. Med.* 8 (4), 261–268.
- Schumann, C., Lenz, G., Berghöfer, A., Müller-Oerlinghausen, B., 1999. Non-adherence with long-term prophylaxis: a 6-year naturalistic follow-up study of affectively ill patients. *Psychiatry Res.* 89 (3), 247–257.
- Scott, J., Pope, M., 2002. Nonadherence with mood stabilizers: prevalence and predictors. *J. Clin. Psychiatry* 63, 384–390.
- Scott, J., Colom, F., Pope, M., 2012. The prognostic role of perceived criticism, medication adherence and family knowledge in bipolar disorders. *J. Affect. Disord.* 142, 72–76.
- Selvakumar, N., Menon, V., Kattimani, S., 2018. A cross-sectional analysis of patterns and predictors of medication adherence in bipolar disorder: single center experience from South India. *Clin. Psychopharmacol. Neurosci.* 16, 168–175.
- Sharma, S., Kumar, N., Chakraborti, S., Sinha, S., Kumari, S., Gajendragad, J.M., 2012. Prevalence and factors associated with medication compliance in Indian patients suffering from mental disorders. *Trop. Doct.* 42 (1), 28–31.
- Sing, Lee, Wing, Y.K., Wong, K.C., 1992. Knowledge and compliance towards lithium therapy among Chinese psychiatry patients in Hong Kong. *Aust. N. Z. J. Psychiatry* 26, 444–448.
- Subramanian, K., Kattimani, S., Sarkar, S., Rajkumar, R.P., 2016. Current adherence attitudes can reflect the course and outcome of bipolar disorder-type I. *Asian J. Psychiatr.* 20, 11.
- Sylvia, L.G., Reilly-Harrington, N.A., Leon, A.C., Kansky, C.I., Calabrese, J.R., Bowden, C.L., et al., 2014. Medication adherence in a comparative effectiveness trial for bipolar disorder. *Acta Psychiatr. Scand.* 129 (5), 359–365. <https://doi.org/10.1111/acps.12202>.
- Thompson, K., Kulkarni, J., Sergejew, A.A., 2000. Reliability and validity of a new medication adherence rating scale (MARS) for the psychoses. *Schizophr. Res.* 42, 241–247.
- Tibrewal, P., Ng, T., Bastiampillai, T., Dhillon, R., Koh, D.H., Kulkarni, S., 2019. Why is lithium use declining? *Asian J. Psychiatr.* 43, 219–220.
- Tse, S., Ng, R.M., 2014. Applying a mental health recovery approach for people from diverse backgrounds: the case of collectivism and individualism paradigms. *J. Psychosoc. Rehabil. Ment. Health* 1, 7–13.
- Won, E., Kim, Y.K., 2017. An oldie but goodie: lithium in the treatment of bipolar disorder through neuroprotective and neurotrophic mechanisms. *Int. J. Mol. Sci.* 18 (12), 2679.
- Yatham, L.N., Kennedy, S.H., Parikh, S.V., Schaffer, A., Beaulieu, S., Alda, M., O’Donovan, C., MacQueen, G., McIntyre, R.S., Sharma, V., 2013. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder. *Bipolar Disord.* 15 (1), 1–44.