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Medication Adherence in a Comparative Effectiveness Trial for Bipolar Disorder

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Abstract

Objective—Psychopharmacology remains the foundation of treatment for bipolar disorder, but medication adherence in this population is low (Range = 20% to 64%). We examined medication adherence in a multi-site, comparative effectiveness study of lithium.

Method—The Lithium Moderate Dose Use Study (LiTMUS) was a six-month, six-site, randomized effectiveness trial of adjunctive moderate dose lithium therapy compared to optimized treatment in adult outpatients with bipolar I or II disorder (N=283). Medication adherence was measured at each study visit with the Tablet Routine Questionnaire.

Results—We found that 4.50% of participants reported missing at least 30% of their medications in the past week at baseline and non-adherence remained low throughout the trial (< 7%). Poor medication adherence was associated with more manic symptoms and side effects as well as lower lithium serum levels at mid- and post-treatment, but not with poor quality of life, overall severity of illness, or depressive symptoms.

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Conclusion—Participants in LiTMUS were highly adherent with taking their medications. The lack of association with possible predictors of adherence, such as depression and quality of life, could be explained by the limited variance or other factors as well as by not using an objective measure of adherence.

Keywords

bipolar disorder; compliance; psychopharmacology

Introduction

Psychopharmacology is the foundation of acute and maintenance treatment for bipolar disorder. However, despite advances in the understanding and availability of effective pharmacological treatments, the pattern of low adherence rates presents an obstacle in the effective study and treatment of bipolar disorder (1). For example, poor medication adherence was the primary reason for early termination among bipolar patients randomized to 6 months of lithium monotherapy or lithium and divalproex combination treatment (2). Specifically, of the 149 patients enrolled into the open-label acute stabilization phase, 42% discontinued prematurely due to poor adherence. Poor adherence to medication also has an impact on both clinical and safety outcomes of bipolar patients, including an increased risk of episode relapse, suicide risk, and hospital re-admission (3–11).

Nonadherence rates to medications in patients with bipolar disorder ranges from 20% to 64% in the literature (6, 7, 12–16), with a median prevalence rate reported as 45% for long-term prophylactic pharmacotherapy (12, 17). In randomized clinical trials of bipolar disorder, nonadherence rates are 20 to 35% (4, 16, 17). These adherence rates may range due to the inconsistent manner in which adherence is measured, reported, and defined in the literature. Adherence was once conceptualized as an “all or none” phenomenon, it is more recently understood as a behavioral continuum such that patients can be “partially” adherent. For example, when medication adherence was assessed by using the medication possession ratio (MPR), bipolar patients were categorized into three groups: fully adherent (MPR greater than .80), partially adherent (MPR from more than .50 to .80), and nonadherent (MPR less than or equal to .50). Based on this definition, 24.5% were considered partially adherent and 21.4% were nonadherent (6). Partial adherence is often the result of patients’ own decisions to modify their treatment regimen by taking a lower dosage, sporadically starting and restarting their medications, or discontinuing one of their prescriptions, rather than completely abandoning treatment (5, 18, 19).

Adherence rates also may range due to many clinical and demographic factors. Several predictors of medication non-adherence have been identified, but some have been more consistently associated with higher rates of non-adherence among individuals with bipolar disorder, such as, comorbid substance abuse (6, 7, 20, 21). Also, individuals with bipolar disorder who are younger, single or living alone, and have an earlier age of bipolar onset may be more likely to be non-adherent (5, 6, 20, 22). Other findings that are less clearly demonstrated as risk factors of poor adherence include prior suicide attempts, current

anxiety disorder, rapid cycling, non-Caucasian ethnicity, limited clinician or family support, side-effects, and homelessness (7, 9, 14, 20, 22).

Aims of the study

The aim of the current study was to assess medication adherence in a comparative effectiveness trial, or generalizable sample of bipolar disorder. We expected that participants would demonstrate adherence rates typically observed in pharmacotherapy studies (i.e., 40–50%) and that lower adherence rates would be associated with bipolar symptoms and worse functioning.

Material and methods

Overview of Study

LiTMUS was a six-month, six-site, parallel-group, randomized effectiveness trial examining the effectiveness of lithium plus optimized treatment (OPT) versus OPT alone (i.e., without lithium). OPT was openly administered, guideline-informed (23), empirically supported, and personalized pharmacologic treatment based on current symptoms, prior treatment history, and course of disorder. Thus, there were no specific restrictions on medications used in OPT and all participants received OPT, but only those randomized to lithium plus OPT group were allowed lithium as part of their OPT regime. The primary aims of LiTMUS were that participants randomized to Li+OPT, compared to those treated with OPT but without lithium would: 1) experience greater improvement in clinical state (as measured by the Clinical Global Impression for Bipolar Disorder Severity scale (CGI-BP-S) and; 2) require fewer major changes in their treatment over the study duration. Changes in treatment were defined as Necessary Clinical Adjustments (NCAs), or medication adjustments to optimize response and functioning, or to address intolerable side effects.

Medication adherence was determined by missing no more than 30% of all psychotropic medications (i.e., lithium and OPT medications) at weeks 0, 12, and 24 of the study. Clinicians and participants knew the treatment assignments (i.e., lithium plus OPT versus OPT alone), but raters of the study outcomes were blinded. The rationale, design, and methods have been detailed elsewhere (24). This study was approved by the Internal Review Boards at the each of the six study sites.

Participants

Participants (N=283) were included in the LiTMUS study if they: 1) Met DSM-IV Criteria for Bipolar Disorder (Type I or II); 2) Able to give informed consent; 3) Age ≥ 18 years; 4) Women who are of child bearing potential must agree to inform their doctor at the earliest possible time of their plans to conceive as well as to use adequate contraception; 5) Currently symptomatic (i.e., CGI-BP-S ≥ 3); 6) Off of lithium for at least 30 days. The final sample (N=200) included only people who had no missing data.

Participants were excluded if they were: 1) Unwilling/unable to comply with study requirements; 2) Renal impairment (serum creatinine >1.5 mg/dL); 3) Thyroid stimulating hormone over >20% above the upper normal limit; 4) Other contraindication to lithium; 5)

Currently in crisis such that other crisis management should take priority; 6) In need of acute detoxification; 7) Pregnant or breastfeeding; 8) Women of child-bearing potential who are not able to agree to the requirements specified above; 9) Currently prescribed lithium within the past 30 days; 10) Participated in a clinical trial of an investigational drug in past month; 11) Inability to agree to comply with the study procedures; 12) History of lithium toxicity, not due to mismanagement or overdose that required treatment.

Measures

Diagnoses were confirmed with a clinician administered Extended Mini-International Neuropsychiatric Interview, a validated structured diagnostic interview to determine current and lifetime Diagnostic and Statistical Manual-Version IV diagnoses (25, 26). The Structured Clinical Interview for DSM- IV Substance Use Disorder Module, was used to assess substance use disorders because it provided additional detail regarding substance use course specifiers.

For the current study, overall severity of bipolar disorder was measured by the Clinical Global Impressions Scale for use in bipolar illness, Severity Index (CGI-BP-S) (27). The CGI-BP-S is a modified version of the CGI designed specifically for use in assessing global illness severity and change in patients with bipolar disorder. Specific mood symptoms were measured with the Montgomery Asberg Depression Rating Scale (MADRS) (28) and the Young Mania Rating Scale (YMRS) (29). The MADRS is a 10-item clinician-rated measure of depression and the YMRS is an 11-item, clinician-rated measure of manic symptoms. Quality of life was measured with the LIFE-Range of Impaired Functioning Tool (LIFE-RIFT; (30)). The LIFE-RIFT assesses the extent to which psychopathology has impacted current functioning in work, household chores, interpersonal relationships with partner, family, and friends, recreational activities, and life, satisfaction, leisure activities and social relationships). Medication side effects were monitored with the Frequency and Intensity of Side Effects Rating (FISER), a reliable and validated self-report measure of intensity, frequency, and burden of side effects (31). Medication adherence was measured using the TRQ as discussed above. The best measure of partial adherence was failure to take 30% or more of their medications in past month when self-report ratings were compared (32, 33). The TRQ is a self-report questionnaire that has significant associations with objective ratings of past non-adherence, repeated past non-adherence, any non-adherence in the past month, and non-adherence in the past week (p=.03) (33). The TRQ was administered at weeks 0 (baseline), 12 (mid-treatment), and 24 (post-treatment) of the study. Recent studies using the TRQ found that 19.3% to 51.4% of individuals with bipolar disorder were non-adherent (i.e., defined as missing 30% or more of their medication in the past month) (7, 34).

Statistical Analyses

The planned analyses were to examine group differences (i.e., adherent Vs. non-adherent) based on the percentage of doses missed (for all psychotropic medications) in the past week at the baseline visit with a cut-off of 30% (i.e., adherence was thus defined as taking at least 70% of one's psychotropic medications). Pearson correlations of medication adherence (i.e., percentage of doses missed) with key study outcomes to explore possible mediators. To test the relationship of medication adherence (as a continuous variable) with bipolar symptoms

over the study period, we conducted mixed effect models to examine the pooled association of medication adherence (i.e., percent of daily doses missed in the last week) on the repeated assessments (CGI-BP-S, MARDS, YMRS, FISER) at each study visit over the 6-month trial[32]..

Results

We found that 4.50% (9/200, Std error=1.47%) of participants, on average, reported missing at least 30% of their medications in the past week at their baseline visit. Given this high rate of adherence (and thus unequal group sizes), we did not find any significant group differences in demographic and clinical features at baseline (see Table 1). Non-adherence remained low throughout the trial, such that at mid-treatment (week 12) 6.45% of participants (17/248, std error=1.56%) missed at least 30% of their daily doses and by the end of the study (week 24) 6.72% (16/238, std error=1.62%) were non-adherent.

Self-reported medication non-adherence (i.e., percentage of doses missed in the past week) was associated with more manic symptoms (YMRS) at mid- (week 12) and post-treatment (week 24) (r = .21 and .14, respectively), lower lithium serum levels at mid- and post-treatment (r = −.23 and −27., respectively), and more side effects (FISER) at pre-treatment (r = −.30), but not with poor quality of life (LIFE-RIFT), overall severity of illness (CGI-BP-S), or depressive symptoms (MADRS) over the study duration (all r's<.16, p's >.05). The mixed effects models found that on average across the study visits low medication adherence was associated with significant elevation in depressive symptoms, and a marginal increase in hypomania/mania (p=.06) symptoms as well as overall severity of symptoms (see Table 2).

Given these results, we conducted two post-hoc analyses. First, we found that at mid- and post-treatment individuals who appeared non-compliant based on their serum lithium levels (i.e., ≤ 0.2) in the Li+OPT group did report more missed doses ($t_{1,102}$ = 2.33, p<.05; $t_{1,101}$ = 3.62, p<.001, respectively). Second, we found that the intraclass correlation (ICC) was 0.22 indicating that within-subject self-reported adherence was quite variable over time suggesting that there was no consistent pattern of endorsed adherence or adequate change in responses on this study variable.

Discussion

LiTMUS yielded remarkably high medication adherence rates (i.e., > 93% over the study duration on average). These data are supported by the association of self-report and objective ratings (i.e., lithium levels) of adherence as well as variability in responses that suggest accurate reporting. Given the high rates of adherence, we did not find any group differences on demographic or clinical features, but we did find that medication adherence was associated with improved course of illness (i.e., fewer symptoms, better overall severity of illness and functioning).

The high rates of medication adherence in LiTMUS is consistent with our data that participants were adherent to the study procedures as highlighted by a high retention rate (i.e., 84%) for the study (36). We discussed several possibilities for this high retention rate

which are applicable here, such as, excellent quality of care with limited participant burden, frequent visits (i.e., every other week for the first half of the study) with their doctors as well as allowing participants to remain in the study regardless of whether they were adherent to the study medication. The high rates of adherence may also be due to using moderate (or perhaps, more tolerable) doses of lithium as well as participants willingness to be in a psychopharmacology study, particularly to test the efficacy of lithium; however, the LiTMUS adherence rates are substantially higher than other bipolar pharmacology trials (37).

Limitations to this study include not having an objective rating of medication adherence in the OPT only group as well as measures to assess participants reasons for choosing to take medications versus not, particularly at the time that participants make these decisions. Our data also suggest that a larger sample is needed to examine medication adherence in individuals with bipolar disorder. Given that this is a treatment seeking population that voluntarily participated in a study to examine the efficacy of lithium, we can not assume that these data are generalizable. However, efforts where made by the investigators to maximize generalizability, such as, having few inclusion/exclusion criteria, paying for treatment as needed (to allow participants in the study who did not have health insurance), and advertising for the study.

Despite these limitations, we found that medication adherence was associated with course of illness in bipolar disorder (6, 8, 37–39). We also found that partial medication adherence (i.e., taking at least 70% of one's daily doses) can be quite high for individuals with bipolar disorder, contrary to previous studies; however, some participants are still not taking their medications even in a closely monitored clinical trial. Thus, these data highlight the need to further elucidate who tends to adhere to their medications, or perhaps more importantly, who does *not* tend to adhere, given that adherence may buffer against future bipolar episodes.

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Declaration of interest

Dr. Sylvia was a shareholder in Concordant Rater Systems and serves as a consultant for Bracket Global, Inc and Clintara. She also receives royalties from New Harbinger Publishers.

Dr. Reilly-Harrington receives royalties from Oxford University Press, the American Psychological Association, and New Harbinger. She serves as a consultant for United Biosource Corporation and was a shareholder in Concordant Rater Systems.

Dr. Leon served on independent Data and Safety Monitoring Boards for AstraZeneca, Sunovion, and Pfizer. He served as a consultant and advisor to FDA, NIMH, MedAvante, and Roche and had equity in MedAvante.

Ms. Kansky has no declarations of interest.

Dr. Calabrese receives federal funding from the Department of Defense, Health Resources Services Administration, and NIMH; he receives research funding or grants from the following private industries or nonprofit funds: Cleveland Foundation, NARSAD, and Stanley Medical Research Institute; he receives research grants from Abbott, AstraZeneca, Cephalon, GlaxoSmithKline, Janssen, Eli Lilly, and Lundbeck; he serves on the advisory boards of Abbott, AstraZeneca, Bristol-Myers Squibb, Dainippon Sumitomo Pharma, Forest, France Foundation, GlaxoSmithKline, Janssen, NeuroSearch, OrthoMcNeil, Repligen, Schering-Plough, Servier, Solvay/

Wyeth, Takeda, and Supernus Pharmaceuticals; and he reports CME activities with AstraZeneca, Bristol-Myers Squibb, France Foundation, GlaxoSmithKline, Janssen, Johnson & Johnson, Schering-Plough, and Solvay/Wyeth.

Dr. Bowden is a research collaborator with Elan and a consultant with Teva, He has no participation with speaker bureaus, nor does he or his wife hold any equity position in any biomedical or pharmaceutical corporation.

Dr. Ketter, between May 14, 2010 and May 14, 2013, had the following financial interests/arrangements or affiliations that could be perceived as real or apparent conflicts of interest: Grant/Research Support from the AstraZeneca Pharmaceuticals LP, Cephalon Inc., Eli Lilly and Company, Pfizer Inc., and Sunovion Pharmaceuticals; Consultant Fees from Allergan, Inc., Avanir Pharmaceuticals, Bristol-Myers Squibb Company, Cephalon Inc., Forest Pharmaceuticals, Janssen Pharmaceutica Products, LP, Merck & Co., Inc., Sunovion Pharmaceuticals, Teva Pharmaceuticals; Lecture Honoraria from Abbott Laboratories, Inc., AstraZeneca Pharmaceuticals LP, GlaxoSmithKline, and Otsuka Pharmaceuticals; and Publication Royalties from American Psychiatric Publishing, Inc. In addition, Dr. Ketter's spouse is an employee of and holds stock in Janssen Pharmaceuticals

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Dr. Iosifescu receives grant support from NIMH. He is a consultant for CNS Response and Servier.

Dr. Thase has been an advisor/consultant: to Alkermes, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Forest Laboratories, GlaxoSmithKline, Janssen Pharmaceuticals, Lundbeck, MedAvante, Merck, Mylan, Neuronetics, Otsuka, Pamlab, PharmaNeuroboost, Pfizer, Rexahn, Roche, Shire, Sunovion, Supernus, Takeda, and Teva, as well as the US Food and Drug Administration and the National Institute of Mental Health. During the same time frame, Dr. Thase has received honoraria for talks from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Merck, and Pfizer and he has received research grants from Alkermes, AstraZeneca, Eli Lilly, Forest, GlaxoSmithKline, Otsuka, PharmaNeuroboost, and Roche, as well as the National Institute of Mental Health and the Agency for Healthcare Research and Quality.

Dr. Ostacher has served as a consultant for Alexza Pharmaceuticals, Janssen, BMS, Eli Lilly, Otsuka Pharmaceuticals, and Sunovion.

Dr. Keyes has no declarations of interest.

Mr. Rabideau has no declarations of interest.

Dr. Nierenberg is a consultant for Abbott Laboratories, Astra Zeneca, Basilea, BrainCells Inc., Brandeis University, Bristol-Myers Squibb, Cephalon, Corcept, Eli Lilly & Co., Forest, Genaissance, GlaxoSmithKline, Innapharma, Janssen Pharmaceutica, Jazz Pharmaceuticals, Lundbeck, Merck, Novartis, PamLabs, PGx Health, Pfizer, Ridge Diagnostics, Roche, Sepracor, Schering-Plough, Shire, Somerset, Sunovion, Takeda, Targacept, and Teva. He is a stakeholder in Appliance Computing, Inc. (MindSite); Brain Cells, Inc., InfoMed (potential share of income). He receives research support from AHRQ, Bristol-Myers Squibb, Cederroth, Cyberonics, Elan, Forest Pharmaceuticals, GlaxoSmithKline, Janssen Pharmaceutica, Lichtwer Pharma, Eli Lilly, Mylin (formerly Dey Pharmaceuticals), NARSAD, NIMH, Pamlabs, Pfizer, Shire, Stanley Foundation, and Wyeth-Ayerst. Honoraria include MGH Psychiatry Academy in the past 3 years (Prior to 3 years ago, honoraria from Bristol-Myers Squibb, Cyberonics, Forest Pharmaceuticals, GlaxoSmithKline, Eli Lilly, Shire, Wyeth-Ayerst). Dr. Nierenberg receives other income from legal case reviews for CRICO, MBL Publishing for past services as Editor-in-chief of CNS Spectrums, Slack Inc. for services as Associate Editor of Psychiatric Annals, and Editorial Board, Mind Mood Memory, Belvior Publications. He has copyright joint ownership with MGH for Structured Clinical Interview for MADRS and Clinical Positive Affect Scale and additional honoraria from ADURS, American Society for Clinical Psychopharmacology and Zucker Hillside Hospital and Forest and Janssen, Biomedical Development, Boston Center for the Arts, University of Pisa, University of Wisconsin at Madison, University Texas Southwest at Dallas, Health New England and Harold Grinspoon Charitable Foundation and Eli Lilly and AstraZeneca, Brandeis University, International Society for Bipolar Disorder, 2nd East Asian Bipolar Forum, Mid-Atlantic Permanente Research Institute, Up-to-Date.

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Significant Outcomes

- Medication adherence in this comparative effectiveness study of lithium for individuals with bipolar disorder was remarkably high
- The high adherence was perhaps due to participants volunteering to participate in this treatment as well as specific aspects of the study design.
- This study furthers our understanding of medication adherence in bipolar disorder as well as how it is associated with course of illness.

Limitations

- This study did not use an objective rating of medication adherence (i.e., pill counting) nor assessed participants' reasons for choosing to take (or not take) their medications.
- Data were also collected during a research trial and thus, may not be generalizable to outpatient treatment of bipolar disorder.

Table 1

Medication Adherence and Baseline Demographic and Clinical Features.

	Adherent Group** (N=191)#	Non-Adherent Group (N=9)#	Test Statistic (df)	P-value
Age				
Mean±SD (N)	39.9±12.0 (191)	40.3±14.1 (9)	0.01 (1)	0.925
Range (min,max)	(18.0,65.0)	(20.0,68.0)		
Median	40.0	37.0		
Gender			2.57 (1)	0.109
Male	39.8% (76/191)	66.7% (6/9)		
Female	60.2% (115/191)	33.3% (3/9)		
Ethnicity			0.24 (1)	0.626
Hispanic or Latino	17.4% (33/190)	11.1% (1/9)		
Not Hispanic or Latino	82.6% (157/190)	88.9% (8/9)		
Marital status			5.13 (4)	0.274
Single	31.9% (61/191)	22.2% (2/9)		
Divorced or separated	23.6% (45/191)	55.6% (5/9)		
Married or living as married	31.4% (60/191)	11.1% (1/9)		
Widowed	2.1% (4/191)	0.0% (0/9)		
Never married	11.0% (21/191)	11.1% (1/9)		
Diagnosis			0.00 (1)	0.955
Bipolar I	77.0% (147/191)	77.8% (7/9)		
Bipolar II	23.0% (44/191)	22.2% (2/9)		
CGI-Severity			0.29 (1)	0.591
Mean±SD (N)	4.3±0.9 (191)	4.1±0.6 (9)		
Range (min,max)	(1.0,7.0)	(3.0,5.0)		
Median	4.0	4.0		
MADRS			0.09 (1)	0.764
Mean±SD (N)	22.2±10.3 (191)	21.1±11.0 (9)		
Range (min,max)	(2.0,49.0)	(5.0,36.0)		
Median	23.0	23.0		
YMRS			0.10 (1)	0.757
Mean±SD (N)	12.8±7.9 (191)	13.7±8.5 (9)		
Range (min,max)	(0.0,39.0)	(2.0,28.0)		
Median	12.0	15.0		
LIFE-RIFT			0.11 (1)	0.735
Mean±SD (N)	20.8±6.4 (191)	20.1±4.5 (9)		
Range (min,max)	(6.0,37.0)	(14.0,25.0)		
Median	20.0	22.0		
Suicide Attempts			0.05 (1)	0.825
Yes	40.7% (77/189)	44.4% (4/9)		
No	59.3% (112/189)	55.6% (5/9)		
Any Anxiety Disorder			1.31 (1)	0.252

	Adherent Group** (N=191)#	Non-Adherent Group (N=9)#	Test Statistic (df)	P-value
No	36.6% (70/191)	55.6% (5/9)		
Yes	63.4% (121/191)	44.4% (4/9)		
Any Substance Disorder			1.46 (1)	0.226
No	46.1% (88/191)	66.7% (6/9)		
Yes	53.9% (103/191)	33.3% (3/9)		

Note.

** Adherence is defined as missing less than 30% of their daily medication doses.

sample was reduced from 283 to 200 due to missing TRQ data at baseline.

Table 2

Mixed Effects Models of Clinical Features and Medication Non-adherence

	Estimate	Std Error	df	*t*	95% CI
CGI-BP-S	1.24	0.35	1059	3.56**	[0.56, 5.39]
YMRS	0.12	0.07	1058	1.87*	[−0.01, 0.25]
MADRS	0.14	0.04	1058	3.35**	[0.06, 0.22]
LIFE-RIFT	0.16	0.18	155	0.85	[−0.21, 0.52]
FISER: frequency	−0.33	0.23	1032	−1.43	[−0.79, 0.12]
FISER: intensity	−0.19	0.26	1033	−0.74	[−0.71, 0.32]
FISER: interference	0.05	0.29	1033	0.16	[−0.53, 0.62]

Note. Clinical Global Impressions Scale for use in bipolar illness, Severity Index (CGI-BP-S); Young Mania Rating Scale (YMRS); Montgomery Asberg Depression Rating Scale (MADRS); LIFE- Range of Impaired Functioning Tool (LIFE-RIFT); Frequency and Intensity of Side Effects Ratings (FISER).

* $p = .06$,

** $p < .01$