Factors Associated With Prospective Long-Term Treatment Adherence Among Individuals With Bipolar Disorder

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Objective: Clinical characteristics, adverse effects of medication, and treatment attitudes have been associated with adherence in bipolar populations in cross-sectional studies. The aim of this secondary analysis from a larger study was to identify the association between baseline variables and average treatment adherence over a subsequent three-year period. *Methods:* Veterans with bipolar disorder were evaluated on self-reported adherence status at baseline and every six months over a three-year period. The sample was dichotomized into two clinically relevant categories: those who were primarily adherent and those who were primarily nonadherent. Demographic and clinical variables were examined for the two groups of patients in relation to their average adherence over the three-year period. *Results:* The study recruited a sample of 306 persons with severe bipolar disorder. The sample was predominantly male (278 men, or 91%), with a mean±SD age of 46.6±10.1 years. A total of 240 individuals (78%) were largely adherent to treatment, and 37 individuals (12%) were largely nonadherent to treatment. Nonadherent individuals were less likely to be on intensive somatotherapy regimens (p=.001); experienced more barriers to care, including lack of telephone access (p<.05) and life obligations and commitments (p<.05); and had more prior suicide attempts (p=.003). *Conclusions:* Nonadherent individuals with bipolar disorder received less intensive pharmacologic treatments, had more suicide attempts, and experienced more barriers to care than adherent individuals. Nonadherence may have system as well as patient components. Consideration of nonadherence as a function of both patient factors and system factors will enhance our ability to understand nonadherence and intervene more effectively. (*Psychiatric Services* 59:753–759, 2008)

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Bipolar disorder is a severe and recurrent mental disorder that is the sixth leading cause of disability worldwide among people 15–44 years of age. It is associated with a greater degree of disability than several prominent chronic medical conditions, including osteoarthritis, HIV infection, diabetes, and asthma (1). There is growing consensus that one of the most difficult and pervasive obstacles to good outcomes among persons with serious mental illness, including those with bipolar disorder, is the individual's discontinuation of medications (2–4). Studies evaluating the extent of nonadherence among bipolar populations report that approximately 20%–70% of patients are poorly adherent with medications (3,5–9).

Medication adherence in bipolar populations is a complex phenomenon that is influenced by a number of illness, patient, provider, and system factors (5,10–15). Age, gender, psychosocial supports, symptom severity, psychiatric comorbidity, medication-related adverse effects, and attitudes toward medication and treatment have all been associated with adherence status (9). Models of health behaviors that focus on determinants of adherence note the importance of personal illness attribution and understanding the effect of experience on an individual's health beliefs. These include perceptions of susceptibility to illness, perceived severity of

illness, the benefits of treatment, the costs and burdens of treatment, and cues to action that may promote treatment adherence (9,16–19). Individuals with bipolar disorder face various barriers that may compromise treatment adherence, including difficulties in understanding and remembering complex medication regimens, side effects from medications, issues of treatment cost and access, difficulties in navigating an often complicated health care system, and stigma related to having mental illness and requiring treatment (9). Identification of potentially modifiable factors that predict treatment adherence is critical in order to develop effective interventions for adherence enhancement in bipolar populations.

A cross-sectional analysis of factors associated with treatment nonadherence in a bipolar veteran population suggested that current substance abuse, disability status, and number of irregular hospital discharges were more common among veterans who were nonadherent compared with those who were adherent (20). Although there is a fairly substantial body of data regarding cross-sectional adherence prevalence and predictors in seriously mentally ill populations, prospective and longitudinal adherence data are much more limited (21,22), and the longitudinal adherence data available are primarily from populations with schizophrenia (21, 23). However, factors that are associated with nonadherence over time may be of particular importance with respect to identifying individuals who might be at greatest risk of nonadherence and may aid in the development of future interventions that could enhance treatment adherence in these high-risk groups.

This secondary longitudinal analysis of self-reported treatment adherence is part of a larger study involving veterans with bipolar disorder participating in a randomized, multicenter research trial (24,25) and follows our baseline assessment of the same sample (20). The aim of this secondary analysis from a larger study was to identify the association between baseline variables and average treatment adherence over a subsequent three-year period. We hypothesized

that veterans with no current substance abuse, those on disability, and those on more intensive medication regimens would be more adherent with bipolar medication treatments over time compared with bipolar individuals who are nonadherent.

Methods

Participants

Participants were recruited as part of Department of Veterans Affairs (VA) Cooperative Study 430, Reducing the Efficacy-Effectiveness Gap in Bipolar Disorder, a three-year, 11-site randomized controlled trial of a collaborative care model versus usual VA care (24–26). This study by design recruited a sample with minimal inclusion and exclusion criteria (patients were not excluded on the basis of currently co-occurring medical illness or substance use disorder) in order to represent as closely as possible the population of veterans with bipolar disorder seen in VA clinical practice. All participating VA sites were solicited through a VA medical center research office and were required to have 24-hour emergency service availability as well as to be in the top three quartiles nationally of mental health visits per patient per year. Among 50 VAs that met these criteria, 12 VAs were chosen to ensure diversity of geographic location, urban versus rural setting, mission, size, and research productivity (24,25). Participants were recruited as inpatients, randomly assigned to a study group at time of discharge, and then followed prospectively for three years. The study was approved by the VA Perry Point Cooperative Studies Human Rights Committee and the institutional review boards of all sites selected.

Participants who met inclusion criteria had a diagnosis of bipolar disorder type I or type II according to *DSM-IV* (27) criteria; an index episode of manic, major depressive, or mixed episode by *DSM-IV* criteria that required hospitalization on an acute psychiatric ward; and at least two hospitalizations on acute psychiatric wards more than three months apart over the prior five years. Exclusion criteria included moderate to severe dementia with a Mini-Mental

State Examination (MMSE) (28) score of less than 26, unresolved substance intoxication or withdrawal, hospitalization on chronic or acute psychiatric wards for six months or more in the past year, and ongoing enrollment in mental health programs with a mobile outreach component in which clinical caregivers deliver services to the patient in the community. Participants were entered into the study between January 1, 1997, and December 31, 2000.

Assessment battery

Intake assessment included informed consent as approved by each site's institutional review board followed by the Structured Clinical Interview for DSM-IV (SCID) (29) as well as a battery of interview and self-report instruments.

SCID interrater reliability (including differentiation of bipolar from substance-induced symptoms) was good to excellent across the sites, including for bipolar diagnosis (Cramér's V=.98), index episode polarity (V=.83), psychosis (V=.65), comorbid current (V=.93–.97) and lifetime (V=.91–.98) anxiety disorders, and current (V=.94) and lifetime (V=1.00) substance use disorders. On the Global Assessment Scale (GAS), the Shrout-Fleiss intraclass correlation coefficient was .86.

The assessment battery included standardized demographic and clinical summaries, the GAS, Somatotherapy Index, Patient Satisfaction Index (30), and the Medical Outcomes Study Short Form–36 (SF-36) (31) subscales for physical health and mental health. The Somatotherapy Index measures mood-specific pharmacotherapy, based on a similar measure used in the 1970s by the National Institute of Mental Health Collaborative Study on the Psychobiology of Depression (32) updated for current guideline-concordant pharmacotherapy specifically for bipolar disorder (26). An update and a validation study are also described elsewhere (26).

Prospective assessments methodology is reported in detail elsewhere (24,25). Briefly, the number of weeks in any affective episode, weeks depressed, and weeks manic or hypo-

manic were derived from longitudinal interval follow-up examinations (LIFE) that were administered every eight weeks (33). The number of medical diagnoses was identified as described by Fenn and colleagues (34). The Working Alliance Inventory is a 36-item self-report instrument that evaluates a patient's perception of treatment relationship (treatment alliance) with his or her provider (35). Items enable evaluation of various domains within the treatment alliance, including perceived acceptance of, trust in, and confidence in the treating clinician. Providers here were clinicians who were identified as an individual's primary mental health clinician, and patients were aware that this information was not to be shared with their clinician. The Patient Satisfaction Index is a self-report instrument originally developed for use with primary care patients and adapted for use with mental health clinic patients of varied educational and socioeconomic backgrounds (30).

Existing survey items and relevant empirical and theoretical literature were reviewed to generate a pool of 29 items constituting barriers to care. Items included the general areas of telephone communication barriers, travel barriers, home obligations and commitments and lack of home support for care, difficulties navigating the clinical site, lack of timely appointments, pharmacy problems, and communication difficulties with providers (36).

Treatment adherence status

Treatment adherence was evaluated via interview during the index hospitalization (20) and every six months for three years. Patients were queried regarding adherence with prescribed medication for the past 30 days. Patients were assured that their response to this query would be confidential and would not be shared with their physician or nurse. Medication adherence scores were derived from five possible patient responses: 1, never missed medication; 2, missed medication a couple of times but took at least 90% of prescribed doses; 3, missed medication several times but took at least half of the prescribed doses; 4, took less than half of the pre-

scribed dose; or 5, stopped taking all medication. Because of the potential impreciseness of self-report, individuals were grouped into two clinically relevant categories that represent the two poles of treatment adherence and are consistent with a similar previous theoretical approach used to evaluate cross-sectional baseline treatment adherence in this sample (20): those who were primarily nonadherent (mean medication adherence score of 3.5 or greater), and those who were primarily adherent (mean medication adherence score of 2.5 or less).

Statistical analysis

Six-month medication adherence scores for every patient were averaged over the three-year length of the trial, and the patients with a mean medication adherence score of 2.5 or less were classified as having good adherence to medication, whereas patients with a mean medication adherence score 3.5 or higher were classified as patients with poor adherence to medication. Baseline adherence scores were not included in the three-year averaged score. Of 277 analyzable patients, 240 (87%) had good adherence and 37 (13%) had poor adherence. There was no difference between adherence among groups that received the larger study intervention and control groups, so the groups were combined for the subsequent analyses.

A two-stage analytic plan to identify significant correlates of prospectively rated adherence was implemented, as we have done in previous studies (37,38). In the first stage, adherence data along with a set of demographic variables (age, age at onset of illness, ethnicity, gender, marital status, education, employment status, and social class), a set of symptom variables (bipolar and other symptoms—including weeks in episode, weeks manic, and weeks depressed—type of bipolar disorder, presence of rapid cycling, presence of psychosis, current and lifetime anxiety, current and lifetime substance abuse, and GAS and SF-36 scores), and a set of treatment-related variables (study termination or completion status, prior hospitalizations, irregular hospital discharges, Somatotherapy In-

dex scores, patient and clinician Working Alliance Inventory scores, and Patient Satisfaction Index score) were assessed in independent bivariate analyses to establish possible association with patients' prospective medication treatment adherence. Mean scores for the continuous variables and proportions of patients for the categorical variables were compared between the good- and poor-adherence groups to identify statistically significant associations on the basis of t tests and chi square analyses, respectively. In the second stage, variables preliminarily tested as univariates using a threshold of .1 were entered into a multivariate analysis with adherence as a dependent variable (logistic regression) and significance set at .05.

Results

Baseline and overall samples

Detailed sample demographic and clinical characteristics and primary trial analyses including participant screening and enrollment flow, have been reported in detail elsewhere (24,25). The study identified 1,231 eligible individuals. Of these, 901 refused random assignment, and 330 were randomly assigned with analyzable data from 306 study participants (24). Twenty-seven percent of eligible individuals were enrolled. As expected in this VA sample, the population was predominantly male (278 men, or 91%), and the mean age was 46.6± 10.1 years. Nearly a quarter (71 persons) belonged to racial-ethnic minority groups, and 265 persons (87%) had type I bipolar illness with an age at onset of 21.0±9.0 years. A total of 240 individuals (78%) were largely treatment adherent (mean medication adherence score of 2.5 or lower), 29 (10%) had intermediate adherence, and 37 individuals (12%) were largely treatment nonadherent (medication adherence score of 3.5 or higher).

Treatment adherence outcomes

Table 1 outlines demographic and clinical characteristics of individuals who were adherent and those who were nonadherent. Most demographic and clinical variables, such as age, gender, ethnicity, symptom severity,

Table 1

Predictors of mean treatment adherence over three years among veterans with bipolar disorder

Variable	Adherent[a] (N=240) N	%	Nonadherent[b] (N=37) N	%	p
Age (M±SD)	44.7±10.0		46.8±10.2		ns
Age at illness onset	20.8±9.1		22.7±8.9		ns
Caucasian	183	76	25	68	ns
Male	217	90	35	95	ns
Unmarried	45	19	8	22	ns
Education (>12 years)	227	95	35	95	ns
Employed	76	37	12	44	ns
Social class[c]					ns
1	8	3	2	5	
2	50	21	6	16	
3	66	28	5	13	
4	111	46	23	62	
5	4	2	1	3	
Bipolar symptoms					
Weeks in episode	25.6±27.2		31.3±32.4		ns
Weeks manic	7.2±11.9		11±17.3		ns
Weeks depressed	19.5±23.6		22.2±23.5		ns
Bipolar disorder type I	212	89	30	81	ns
Rapid cycling					
Never	101	43	16	43	ns
Past	26	11	5	13	ns
Current	107	46	16	43	ns
Psychosis present	79	34	15	41	ns
Current anxiety	93	39	13	35	ns
Lifetime anxiety	104	44	16	43	ns
Current substance abuse	10	4	4	11	.1
Lifetime substance abuse	54	23	9	24	ns
Prior suicide attempts	145	61	32	86	.003[d]
Study completers	198	83	33	89	ns
Receiving disability					
Civilian disability	118	49	17	46	ns
Veterans disability	127	53	19	51	ns
Any disability	177	74	27	73	ns
Global Assessment of Functioning[e]	49.8±13.5		47.9±15.9		ns
SF-36[f]					
Physical health component	42.7±10.5		46.1±11.8		.06
Mental health component	34.4±9.9		33.0±10.6		ns
Comorbid medical diagnoses	5.5±4		4.8±3.8		ns
Prior hospitalizations	5.4±5.9		5.1±3.4		ns
Irregular hospital discharges	.5±1.3		.81±1.2		ns
Barriers to care					
Telephone access	6.5±.8		6.8±.7		.05[d]
Travel difficulties	4.9±.5		5.0±.6		ns
Travel distance	6.6±4.6		7.5±9.6		ns
Communication	6.2±.7		6.5±.6		.02
Life commitment barriers	6.9±1.0		7.4±1.4		.09[d]
Total barriers	41.2±5.1		44.2±10.1		ns
Somatotherapy Index[g]	3.1±.9		1.3±.9		<.001
Working Alliance Inventory[h]					
Patient score at week 156	152.6±20.1		149.8±23.2		ns
Clinician score at week 156	150.6±20.1		149.8±23.2		ns
Patient Satisfaction Index[i]	38.3±4.3		37.8±4.0		ns

[a] Mean medication compliance score over time ≤2.5

[b] Mean medication compliance score over time ≥3.5

[c] Hollingshead-Redlich scores, with lower numbers indicating higher social class

[d] Remained significant in multivariate analysis. Variables preliminarily tested as univariates, with a .1 threshold, were entered into a multivariate analysis (excluding the Somatotherapy Index, which is very highly correlated with adherence) that used adherence as a dependent variable (logistic regression) and significance set at .05.

[e] Possible scores range from 0 to 100, with higher scores indicating higher functional status.

[f] Medical Outcomes Study 36-item Short Form; possible scores range from 0 to 100, with higher scores indicating better health.

[g] Possible scores range from 0 to 5, with higher scores indicating more intensive somatotherapy and a score of 3 generally considered adequate.

[h] Possible scores range from 36 to 252, with higher scores indicating better working alliance.

[i] Possible scores range from 12 to 72, with higher scores indicating greater satisfaction.

presence of psychosis or comorbid substance abuse, and functional or general health status, did not differ statistically between adherent and nonadherent groups. However, having had at least one prior suicide attempt was significantly associated with nonadherence (p=.003). Adherent individuals were more likely to be treated with medication regimens of higher intensity (p<.001).

After the preliminary analysis of univariates with a .1 threshold, we ran logistic regression analyses with adherence (good, 0; poor, 1) as the response variable and mean somatotherapy score, prior suicide attempts (yes or no), mean score on the physical components subscale, and three barrier variables—telephone contact, communication, and life commitments—as the independent variables (Table 1). On this planned analysis, mean somatotherapy score was highly correlated with adherence (r=–.54).

On clinical grounds we reasoned that intensity of medication treatment could be a downstream effect of poor adherence (reflecting less success by the treating clinician to manage symptoms and illness). We therefore conducted a second, exploratory multivariate logistic regression to evaluate strength of association between the remaining variables (suicide, physical components score, and three barrier subscales) and treatment adherence. Three variables—prior suicide attempts, telephone access barriers, and life commitment barriers—were found to be significantly associated with three-year adherence status. Patients with prior suicide attempts had very high odds of being poorly adherent (odds ratio [OR]=19.8 with a 95% confidence interval [CI] of 2.4–161.9). In addition, patients with more telephone access problems (OR=2.4, CI=1.2–4.7) and with more life commitments (OR= 1.6, CI=1.1–2.5) had relatively high odds of being poorly adherent.

Discussion

This prospective study, in which we examined the relationship of baseline variables to average adherence to medication during a subsequent three-year period in a bipolar popula-

tion, found that nonadherence was relatively common (just over 12%). This finding is somewhat lower than the nonadherence rates of 20%–35% reported in some randomized controlled trials conducted with patients with bipolar disorder (39–41). The difference may be related to the longer duration of this study and the fact that average adherence over all three years served as the dependent variable. There has been some concern regarding the relevance of patient outcomes from a randomized controlled trial to real-world clinical practice (42). Accordingly this study provided clinically relevant new information because it was designed from the outset as an effectiveness trial (26). The study sample comprised individuals with multiple psychiatric and medical comorbidities. In comparison with other large samples of patients with bipolar disorder, those in our sample were somewhat older, were more severely ill, and had highly complex symptoms (24,25). In relation to the overall veteran population, our sample had a larger proportion of women and persons of racial-ethnic minority groups (26). Participants in this study also had relatively high rates of hospitalization, prior suicide attempts, and disability.

Reasons for nonadherence among bipolar populations are multiple and diverse (43), and reports of treatment nonadherence in the general population of patients with bipolar disorder are in the order of 20%–55%, (13, 44–46), with levels approaching 55% in longitudinal adherence studies (47). In the study reported here, nonadherence was associated with lower-intensity bipolar medication treatment, more barriers to care, and more previous suicide attempts. Demographic and clinical variables, such as age, gender, ethnicity, symptom severity, comorbid substance abuse or anxiety, functional disability status, and general health status, were not different between nonadherent and adherent groups. It is possible that lower-intensity medication treatments by nonadherent individuals may thus reflect difficulties with access to care, at least in part, rather than differences in symptoms or functional status.

A previous cross-sectional, baseline analysis of treatment adherence in this same clinical trial population (20) found that nonadherence by individuals with bipolar disorder was associated with current substance abuse, being on disability status, receiving less intense bipolar medication treatments, and having a history of irregular hospital discharges. It is possible that participation in the longitudinal clinical trial presented here may have diminished some of the effects of substance abuse (or substance use intensity) on individuals participating in this study.

Other investigators have identified a relationship between nonadherence and suicide in bipolar populations (48,49). Baldessarini and colleagues (49) reported that suicidal acts were reduced 6.5-fold per year during lithium treatment of bipolar disorder and that suicide rates rose 20-fold in the first year after ceasing use of lithium. It is possible that in the population presented here, previous suicide attempts could have been related to long-standing nonadherence with medication treatments. Given the previous pattern of attempts at self-harm among bipolar patients, the apparent lack of biologic treatments known to be effective for bipolar disorder is particularly worrisome, and nonadherent individuals with bipolar illness likely represent a group that could be particularly vulnerable to future suicide attempts.

Our findings of increased selected barriers to care among nonadherent bipolar patients suggest that problems with access to care may explain, at least in part, the reduced utilization of medication treatments. This explanation is consistent with our prior proposal that nonadherence can be best understood as a function not of the patient in isolation but rather as part of a complex system that includes both the provider and the health care organization (20). McCarthy and colleagues (50) examined a VA population with serious mental illness and noted that geographic accessibility to care and resource availability were associated with long-term continuity of care and that, conversely, increased distance from providers was associated with greater gaps in health care

use. The greater number of barriers to care among nonadherent individuals with bipolar illness in the study presented here may provide a clue about measures that may enhance adherence in historically nonadherent populations. Findings of this analysis suggest that barriers to access of care, particularly barriers to telephone access, are a reasonable starting place to study further and potentially design future interventions. McCarthy and colleagues (51) have suggested that patients with bipolar disorder and receiving care in the VA may reduce accessibility barriers by "chaining" or coordinating multiple outpatient visits within a single visit to the VA service center. Similarly, pooling of access services for diverse types of health care within one or more networks could lead to reduction in communication or telephone barriers to care.

Previous data on longer-term predictors of nonadherence in mood-disordered populations (9,47) suggest that negative attitudes toward mood-stabilizing medication prophylaxis are a strong correlate of nonadherence to lithium therapy. Although the study presented here did not specifically evaluate attitudes toward long-term medication prophylaxis, it is possible that the relatively low utilization of medication could also be associated with lack of interest in medication prophylaxis in addition to perceived barriers to care. Relationship with providers (working alliance) did not appear to differ between adherent and nonadherent patients in the sample we studied, so any attitudinal differences may have been centered on biologic treatments. The greater number of previous suicide attempts among nonadherent patients suggests that these individuals are possibly more ill overall compared with adherent individuals.

Limitations of this study include the utilization of a sample treated solely within the VA health care system, underrepresentation of women, self-report–based method of adherence assessment, and the inclusion of only participants who agreed to participate in a research study. Although Stephenson and colleagues (52) have suggested that self-report may overestimate adherence rates by about 15%, it is interesting to note that self-report in bipolar disorder appears much more reliable than clinician predictions, which have only 50%–60% accuracy (19). The nonadherent individuals in this study do not represent the most extreme end of the nonadherence spectrum, because those at the most extreme end would likely not agree to participate in a clinical trial.

There were additional limitations. Even though the study retention rate of over 80% over a three-year period is quite good for longer-term bipolar studies, it was not possible to follow adherence status and possible clinical associations for the study population that did not complete the protocol. It must be noted that given the paucity of data on longitudinal adherence predictors in populations with bipolar disorder, the statistical methods used to preliminarily identify positive long-term predictors are exploratory and data should be interpreted with caution. Because multiple comparisons were made in this study it is possible that study findings could be by chance alone. Predictors for long-term adherence need to be confirmed with future studies using a more rigorous design and specific hypothesis testing. Finally, medication and resource use patterns in the VA may differ from those seen in a non-centralized care system, where there may be other restrictions to various health care services, including medications. It is possible that in noncentralized systems, barriers to care may be even more strongly associated with treatment nonadherence.

Conclusions

Compared with adherent individuals, nonadherent individuals with bipolar disorder make more suicide attempts and have more barriers to care and appear to receive less intensive medication treatments than individuals who are adherent with their medications. Additional analyses of the possible relationships between care barriers, intensity of biologic treatments, treatment adherence, and suicide risk are needed to improve treatment outcomes in bipolar populations. Consideration of nonadherence as a function not just of patient factors but also system factors will enhance our ability to understand nonadherence and to intervene more effectively.

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