The Effect of Medication Adherence on Health Care Utilization in Bipolar Disorder

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A retrospective analysis of electronic prescription and medical claims representing approximately 1.4 million managed care commercial health plan members with mental health benefits was conducted. The effect of patient adherence to traditional mood-stabilizer therapy (lithium, valproate, carbamazepine, lamotrigine, or oxcarbazepine) for bipolar disorder on mental health–related hospitalization was assessed among 1,399 patients (mean age, 42.9 yr; 66.3% female) studied. Reduced adherence to traditional mood-stabilizing therapy (< 80%) in patients with bipolar disorder was associated with significantly greater risk of mental health–related, emergency room visits (odds ratio, 1.98; 95% confidence interval, 1.38–2.84) and inpatient hospitalizations (odds ratio, 1.71; 95% confidence interval, 1.27–2.32), even after adjusting for age, gender, and comorbidity.

Bipolar disorder (BD) is a chronic mental health illness characterized by cyclic episodes of depression and mania, with a prevalence rate of approximately 1% in the U.S. adult population.[1] It is associated with significant morbidity, ranking as the sixth leading cause of disability in the world among those aged 15 to 44 years in 1990, and ranking as the fifth leading cause of years lived with disability among the same age group in 2000.[2] Patients with BD may use about four times the health care resources and incur four times the health care charges of the average member in a health plan.[3,4]

Hospitalizations for the disorder result from the need to manage acute mania and to stabilize patients with BD. About two-thirds of patients with BD require multiple hospitalizations during the course of their illness.[5] Not surprisingly, inpatient medical encounters account for the substantial burden of the cost of treating BD.[4] Patients with BD represent about 10% of the adult population that utilize inpatient mental health care, accounting for more than 140,000 hospitalizations in the United States each year.[6]

Unfortunately, no cure exists for BD, and the major goal of acute treatment is resolution of symptoms and subsequent maintenance treatment to prevent future relapses. The recommended medications for all phases of treatment for BD include a mood-stabilizing agent. Lithium, valproate, carbamazepine, lamotrigine, or oxcarbazepine represent traditional mood-stabilizing agents recommended in practice guidelines for the long-term maintenance therapy of bipolar disorder, and they may be used alone or in combination with antipsychotics and antidepressants during the acute phase.[7,8]

Among patients with BD who do receive mood-stabilizing therapy, poor adherence with therapy is a significant factor for poor treatment outcomes and subsequent hospitalization.[9,10] A small prospective study of 98 patients with mood disorders (78 with BD) revealed that self-reported adherence to mood-stabilizing treatment (lithium, carbamazepine, and valproate) was associated with significantly lower admission to a psychiatric hospital compared with partial adherence.[9] In addition, a retrospective claims analysis among 67 patients with BD showed

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lower hospitalization rates with higher adherence to neuroleptics, lithium, and antidepressants.[10] Among patients discharged from a hospitalization for BD, Keck and colleagues[11] reported on a 12-month follow-up study of 134 subjects and demonstrated that medication adherence of at least 75% was associated with a greater likelihood of remission for at least eight contiguous weeks.

The present study investigated the relationship between adherence to traditional mood-stabilizing therapy and mental health–related, emergency room (ER) visits, and inpatient hospitalizations, in a large U.S. population of patients with BD from an MCO.

PATIENTS AND METHODS

Study Design. This study was a retrospective analysis of electronic prescription and medical (including behavioral health carve-out benefit) claims from a large MCO representing approximately 1.4 million commercial health plan members with prescription medication and mental health benefits.

Patient Selection. Patients with at least one primary or secondary diagnosis of BD (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] diagnosis codes 296.0x, 296.1x, 296.4x, 296.5x, 296.6x, 296.7x, 296.8x) were identified from medical claims between January 1 and December 31, 2002 (the identification period), and followed from January 1 through December 31, 2003 (the follow-up period). Patients identified for inclusion who were not continuously enrolled, or who were younger than 18 years on January 1, 2003, were excluded from the investigation. Those who did not receive a traditional mood-stabilizing agent (lithium, valproate, carbamazepine, lamotrigine, or oxcarbazepine) during the calendar year 2003 were also excluded from the analysis, since these agents are included in evidence-based expert consensus guidelines for all phases of treatment for BD.[7,8]

Cohort Definition. Patients meeting the inclusion and exclusion criteria were stratified into two mutually exclusive cohorts based on adherence to traditional mood stabilizers during 2003. Adherence on a mood-stabilizing agent was calculated by summing the total days of supply for a mood-stabilizing agent in 2003 and dividing this sum by 365 days and multiplying by 100 to obtain the adherence percentage. The calculation of days supply began with the last mood-stabilizing agent prescription in 2002 and continued to the last prescription in 2003. Total days of supply were truncated to exclude the period before January 1, 2003 and after December 31, 2003. Patients who were 80% or more adherent to a mood-stabilizing agent were assigned to the "high-adherence" cohort, whereas those with less than 80% adherence were allocated to the "low-adherence" cohort.

Outcome Measures. All medical claims with a primary or secondary diagnosis of a mental disorder (ICD-9-CM diagnosis codes 295.xx, 296.xx, 297.xx, 298.xx, 300.xx, 301.xx, 303.xx, 304.xx, 305.xx, 307.xx, 311.xx, 312.xx) were used to determine the mental health–related outcomes. The primary outcome measures of interest were mental health–related number of ER visits and inpatient hospitalizations, including those to psychiatric facilities, and the mean duration of the hospitalizations. Other psychotropic medication classes received during the one-year review period were also noted, along with physician specialty for the first psychotropic medication prescription filled during 2003. Baseline characteristics examined included age as of January 1, 2003, gender, and comorbidity. Comorbidity was assessed using the Charlson Comorbidity Index (CCI).[12] The CCI contains 19 well-defined diagnoses, with each having an associated weight based on adjusted risk of one-year mortality. A version of the CCI adapted for calculation of the overall CCI score through the use of ICD-9-CM diagnostic codes from electronic claims was used, encompassing 17 medical conditions.[13] The overall CCI score reflects the cumulative increased likelihood of one-year mortality, with a higher score indicating a more severe burden of comorbidity.

Statistical Methods. All data extraction and statistical analyses were performed using SAS (SAS Institute Inc., Cary, NC), version 9.1. Descriptive statistics, including *t* tests and Chi-square tests, were used to compare baseline characteristics and the proportion of members experiencing mental health-related ER visits and inpatient hospitalizations, as well as the duration of mental health–related hospitalizations, between the two adherence cohorts. Mean and standard deviations are reported for continuous variables. Logistic regression models were performed, adjusting for age, gender, and comorbidity, to compare the risks of mental health–related ER visits and inpatient hospital admissions. The adjusted odds ratios and associated 95% confidence intervals were reported. All reported *P* values are two-sided, with an alpha level of .05.

RESULTS

A total of 1,406,414 adult members in the commercial health plan with prescription medication and mental health benefits were reviewed, of which 6,581 were identified as having a BD diagnosis. From this group, 1,399 met the inclusion and exclusion criteria. Among them, 767 (54.8%) were classified into the

low-adherence cohort and 632 (45.2%) were classified into the high-adherence cohort. The overall mean age was 42.9 ± 11.4 years, with the high-adherence group being older on average than the low-adherence group (44.9 yr vs. 41.3 yr, respectively; $P < .0001$). Both adherence groups had similar CCI scores: 0.57 in the low-adherence group versus 0.62 in the high-adherence group. A greater proportion of patients in the 18- to 34-year age group had calculated mood-stabilizing therapy adherence rates of less than 80% (Table I). Overall mean adherence rate to mood-stabilizing therapy in patients with BD during 2003 was 66.3%. The mean adherence rate was 42.8% in the low-adherence cohort and 94.8% in the high-adherence cohort.

The high-adherence cohort demonstrated significantly higher concurrent use of antipsychotic agents than the low-adherence cohort (74.5% vs. 63.5%, respectively; $P < .0001$) and significantly less concurrent utilization of antidepressant medications (70.3% vs. 76.4%, respectively; $P = .0094$). The distribution of physician specialty for the first filled psychotropic prescription during 2003 was similar between the two adherence groups (Table II).

A significantly smaller proportion of patients with BD in the high-adherence group experienced mental health–related ER visits and inpatient hospitalizations during 2003 (Table III). However, among those experiencing a mental health–related hospitalization, the mean duration of inpatient stay was similar between the two adherence groups. After adjusting for age, gender, and comorbidity, patients with BD and with low adherence to mood-stabilizing therapy were almost twice as likely to experience mental health–related ER visits (odds ratio, 1.98; 95% confidence interval [CI], 1.38–2.84) and inpatient hospitalizations (odds ratio, 1.71; 95% CI, 1.27–2.32).

TABLE I: BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS STRATIFIED BY MOOD-STABILIZER MEDICATION ADHERENCE GROUP

Demographic and Clinical Characteristics	Adherence: Low (< 80%)	Adherence: High (≥ 80%)	Total	*P* Value
Cohort Size (N)	767 (54.8%)	632 (45.2%)	1,399	(100.0%)
Female (N)	507 (66.1%)	420 (66.5%)	927 (66.3%)	NS
Age* (yr, mean ± SD)	41.3 ± 11.7	44.9 ± 10.7	42.9 ± 11.4	< .0001
Age Range (yr)				< .0001†
18–34 (N)	220 (28.7%)	111 (17.6%)	331 (23.7%)	
35–49 (N)	357 (46.5%)	314 (49.7%)	671 (48.0%)	
50–64 (N)	181 (23.6%)	196 (31.0%)	377 (27.0%)	
65–79 (N)	9 (1.2%)	10 (1.6%)	19 (1.4%)	
≥ 80 (N)	0 (0.0%)	1 (0.2%)	1 (0.1%)	
Charlson Comorbidity Index (mean ± SD)	0.57 ± 1.25	0.62 ± 1.40	0.59 ± 1.32	NS
Adherence to Mood Stabilizer (%, mean ± SD)	42.8 ± 23.7	94.8 ± 6.3	66.3 ± 31.5	

*As of January 1, 2003.
†Chi-square test with age group 65–79 and ≥ 80 combined
N = Number; NS = not statistically significant; SD = standard deviation.

TABLE II: CONCURRENT PSYCHOTROPIC TREATMENT BY MOOD-STABILIZER MEDICATION ADHERENCE GROUP

Demographic and Clinical Characteristics	Adherence: Low (< 80%)	Adherence: High (≥ 80%)	Total	*P* Value
Cohort Size (N)	767 (54.8%)	632 (45.2%)	1,399 (100.0%)	
Psychotropic Medication				
Antianxiety Agents (N)	289 (37.7%)	210 (33.2%)	499 (35.7%)	NS
Antidepressants (N)	586 (76.4%)	444 (70.3%)	1,030 (73.6%)	.0094
Antipsychotics (N)	487 (63.5%)	471 (74.5%)	95 (68.5%)	< .0001
Sedative/Hypnotics (N)	151 (19.7%)	130 (20.6%)	281 (20.1%)	NS
Physician Specialty Prescribing First Psychotropic Medication				NS
Primary Care (N)	123 (16.0%)	73 (11.6%)	196 (14.0%)	
Psychiatry (N)	310 (40.4%)	275 (43.5%)	585 (41.8%)	
Other (N)	12 (1.6%)	11 (1.7%)	23 (1.6%)	
Unknown (N)	322 (42.0%)	273 (43.2%)	595 (42.5%)	

N = Number; NS = not statistically significant.

DISCUSSION

Use of a mood-stabilizing agent is recommended in all phases (acute and maintenance) of treatment for patients with BD and is important in attaining symptom resolution, restoring function, and achieving remission.[7,8] The fact that a significant proportion of patients with BD are not prescribed or do not fill a prescription for a mood-stabilizing medication is concerning. Fifty-four percent (1,644) of adult subjects with BD, who had otherwise met all other inclusion and exclusion criteria, were excluded from this analysis, because a mood-stabilizing agent was

TABLE III: UNADJUSTED MENTAL HEALTH–RELATED HOSPITALIZATIONS BY MOOD STABILIZER MEDICATION ADHERENCE GROUP DURING THE 12-MONTH FOLLOW-UP PERIOD (2003)

Mental Health–Related Hospitalizations	Adherence		*P* Value
	Low (< 80%)	High (≥ 80%)	
Cohort Size (N)	767 (54.8%)	632 (45.2%)	< .0001
Emergency Room Visits (N)	113 (14.7%)	48 (7.6%)	< .0001
Inpatient Hospitalizations (N)	153 (19.9%)	77 (12.2%)	< .0001
Days of Hospitalization Among Those Hospitalized (mean ± SD)	15.9 ± 28.9	15.6 ± 23.5	NS

N = Number; NS = not statistically significant; SD = standard deviation.

not received during the follow-up period. This finding is similar to that of Li and colleagues,[14] who demonstrated that 58% of patients with BD did not receive a mood-stabilizing agent during the first posttreatment year. Birnbaum and associates[15] found that only 34% of patients with recognized BD were receiving a mood-stabilizing agent.

Among those patients with BD who do receive mood-stabilizing therapy, nonadherence to therapy is a significant factor for poor treatment outcomes and subsequent hospitalization.[9,10] Keck and coworkers[11] followed 134 patients for a 12-month period after hospital discharge (for BD treatment) and demonstrated that full compliance (defined as medication adherence ≥ 75%) was associated with remission for at least eight contiguous weeks. Less than half of the patients studied (47%) by those investigators were considered fully adherent, a finding that is similar to that of the present study, which found only 45% of patients with BD were highly adherent with mood-stabilizing therapy. An 80% cut-off was used to define high adherence in the present study, since an adherence rate of less than 80% equated to missing at least one week of therapy for a typical 30-day prescription fill. Eaddy and associates[16] also used the 80% cut-off to define "compliant" in their assessment of 7,864 patients with schizophrenia or BD, and found that partially compliant patients (adherence < 80%) were 49.0% (95% CI, 29.2%–71.7%) more likely than compliant patients to have an inpatient hospitalization.[16] However, the number of patients with BD compared with schizophrenia in their study was not revealed.

In the present study, the finding of 55% of patients with BD who exhibited low adherence to mood-stabilizing therapy is consistent with the reported nonadherence rates of 23% to 68% in other studies examining medication nonadherence in BD. It adds to the clinical evidence highlighting the substantial problem of medication adherence in the management of patients with BD.[17]

Many factors may contribute to poor adherence in patients with BD, including denial of illness, younger age, treatment side effects, single marital status, low educational level, and substance abuse.[18] Keck and co-workers,[19] in their examination of compliance with mood-stabilizing therapy using a clinician-administered questionnaire, found that patient denial of need was the most common reported reason for noncompliance. Morselli and Elgie,[18] in their survey of 1,041 patients with BD, found that fears regarding drug dependency were a more important reason for nonadherence than treatment side effects.[8] Although the effect of many of these factors could not be evaluated through the present retrospective claims analysis, one factor that was discernable was the lower adherence rate seen with younger age.

The low-adherence group tended to be younger than the high-adherence group by almost four years on average. Two-thirds (66.5%) of those between the ages of 18 and 34 years were in the low-adherence group. Li and colleagues[14] studied a Medicaid population with BD and found better adherence to mood stabilizers in those patients with BD was associated with a previous history of major depression.[14] The present study did not examine for previous history of major depression but did observe the group demonstrating higher adherence to mood-stabilizing therapy had significantly lower concurrent use of antidepressant medications.

This study of a commercial health plan population revealed that mental health–related hospitalizations (ER visits and inpatient admissions) were almost twice as likely in patients with BD who were less adherent to mood-stabilizing therapy. As inpatient medical encounters represent the key burden of the cost of treating BD, interventions aimed at reducing hospitalizations can play a significant role in limiting the cost of treating BD. Two smaller investigations examined the relationship between nonadherence to mood-stabilizing therapy and hospital use and found a similar trend. Svarstad and associates[10] conducted a retrospective examination of a Medicaid population with BD. They defined irregular use of medications (which included lithium, neuroleptics, or antidepressants) as missing a subsequent prescription claim in one or more quarters of the 12-month follow-up. The proportion of patients with BD experiencing a rehospitalization was a little more than two times higher in the group that exhibited irregular use of their medications. However, unlike the finding of a similar length of hospitalization in both the low- and high-adherence groups, Svarstad's group[10] demonstrated a longer

duration of hospitalization in the group with irregular medication use compared with the regular medication-use group, although their study size was limited to 67 subjects with BD. In a prospective study, Scott and Pope[9] reported findings for 98 patients with mood disorder, 78 of whom were diagnosed with BD. Partial adherence was defined as missing 30% or more of prescribed mood-stabilizing therapy (lithium, carbamazepine, or valproate). At 18 months, psychiatric hospital admission rates were highest in the partially adherent group and lowest in the adherent group (therapeutic plasma drug levels checked), although adherence was self-reported.

Limitations. This study, which relied on claims data analysis, possesses certain limitations. Relying on at least one medical claim with a primary or secondary diagnosis of BD could have potentially included more patients (without BD) than was intended. However, this is less likely, given the inclusion requirement that subjects had also initiated a traditional mood-stabilizing agent (lithium, valproate, carbamazepine, lamotrigine, or oxcarbazepine) during the follow-up period. Alternatively, underreporting or miscoding may occur with claims, making possible the chance that some patients with BD were not identified. Although the use of prescription claims eliminated recall bias in assessing adherence, it did not provide a way to confirm that the patients did indeed take their medications. However, it is likely that patients who continued to refill their prescriptions were taking their medication. Relapses and hospitalizations during the follow-up period could have subsequently prompted patients toward improving their adherence to their mood-stabilizer therapy, potentially reducing the difference in hospitalizations observed between the two adherence groups.

Differences in the utilization frequency for each mood-stabilizing agent between the two adherence cohorts were not examined. However, Colom and coworkers[21] previously investigated the clinical factors associated with treatment noncompliance in patients with euthymic BD and found no association between type of medication and compliance.[21] Also, patients switching to an alternative off-label drug therapy for mood stabilization (e.g., gabapentin), if efficacious and adherent with therapy, may have been grouped into the low-adherence group, thereby potentially diminishing the observable difference in hospitalization between the two groups.

Differences in the severity and duration of BD illness between the two cohorts, which could contribute to hospitalization, could not be assessed. Since the baseline measure of comorbidity yielded a similar CCI between the two cohorts, this may not be a significant concern. The present investigation was unable to differentiate whether the prescribed mood-stabilizing agent was being used for treatment of an acute episode or for chronic maintenance treatment of BD. Antipsychotic therapy is currently recommended as concomitant therapy with a mood-stabilizing agent in the revised American Psychiatric Association (Arlington, VA) practice guidelines for the acute management of a severe manic or mixed episode, or as monotherapy in less-ill patients.[8] However, antipsychotic therapy is absent from the recommendations for chronic maintenance therapy in patients with BD.[8] This study demonstrated greater use of antipsychotic therapy in the high-adherence group that experienced fewer ER visits and inpatient hospitalizations, with almost three-quarters of patients in the high-adherence group having a prescription fill for an antipsychotic agent during the follow-up period.

Despite the aforementioned limitations associated with analyses relying on electronic health care claims databases, its availability within most MCOs provides many opportunities for those organizations to examine their population and validate these findings. Future studies are needed to assess the effect of concurrent antipsychotic therapy on the risk for hospitalization in patients with BD.

CONCLUSIONS

Despite consensus and practice guidelines that recommend the use of mood-stabilizing agents for patients with BD, this study reconfirmed the underutilization of these agents in this patient population. Additionally, the majority of patients with BD who did receive a mood-stabilizing agent demonstrated poor adherence. In patients with BD, better adherence to mood-stabilizing therapy was associated with significantly lower risk of mental health–related ER visits and inpatient hospitalizations. Efforts aimed at improving use of and adherence to mood-stabilizing therapy in patients with BD may lead to reduced mental health–related hospitalizations and improved patient outcomes.

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