Misdiagnosed Patients With Bipolar Disorder: Comorbidities, Treatment Patterns, and Direct Treatment Costs

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Objective: The purpose of this study was to examine comorbidities, treatment patterns, and direct treatment costs of patients with bipolar disorder who are misdiagnosed with unipolar depression.

Method: This study is a retrospective analysis of data from the MarketScan Commercial Claims and Encounters (CCE) database. Logistic regressions and analyses of variance were used to compare the misdiagnosis cohort to 3 age- and gender-matched comparison cohorts (recognized bipolar, depression, and no psychiatric disorders based on ICD-9-CM criteria) during the year 2000.

Results: Each cohort had 769 individuals (68.0% female; mean age of roughly 42 years). The misdiagnosis cohort had higher rates of several psychiatric comorbidities than the depression cohort (e.g., personality disorders, alcohol abuse, psychotic disorder) and the bipolar cohort (e.g., generalized anxiety disorder, panic) but a lower rate of psychotic disorders than the bipolar cohort ($p < .05$). Compared with the bipolar cohort, the misdiagnosis cohort was more likely to receive antidepressants, but less likely to receive anticonvulsants, antipsychotics, or lithium (all $p < .001$). Antidepressant rates were similar among the misdiagnosis and depression cohorts. Group differences were found in mean annual costs for anticonvulsants, antipsychotics, lithium, antidepressants, and total treatment costs: bipolar ($442, $310, $67, $497, $8600); misdiagnosis ($221, $185, $20, $704, $8761); depression ($70, $74, $5, $657, $7288).

Conclusion: Misdiagnosed bipolar patients received inappropriate and costly treatment regimens involving overuse of antidepressants and underuse of potentially effective medications. Patterns of psychiatric comorbidity suggest one possible strategy for improving recognition of bipolar disorder among patients presenting with depressive symptoms. Patients who present with the observed pattern of comorbidities may benefit from additional screening for bipolar disorder. It is recommended that steps be taken to minimize misdiagnosis in clinical settings.

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Lifetime prevalence rates of bipolar disorder in primary care and general population samples range from roughly 0.5% to 5%, depending on the disorder subtypes and the diagnostic approach.[1–3] This common psychiatric disorder has been shown to impair patients' quality of life and functional status, including occupational functioning.[2,4–6] For some patients, bipolar disorder may be fatal, as it has been linked to high rates of suicide attempts and suicidal ideation.[7,8] Bipolar disorder is also associated with greater health care service utilization and direct medical costs than unipolar depression.[2,4,9,10]

Pharmacologic and psychosocial treatments can often reduce the tremendous burden of this disorder on patients and the health care system.[11–16] However, a growing body of research indicates that misdiagnosis of patients with bipolar disorder is a common barrier to effective treatment. Two surveys of members of the National Depressive and Manic-Depressive Association (DMDA)[17,18] provide compelling evidence that misdiagnosis of bipolar disorder is a widespread problem. In the first survey of 500 bipolar patients conducted in 1992,[17] 73% of respondents reported receiving an alternative explanation of their symptoms before being diagnosed with bipolar disorder. Of these 500 respondents, 48% consulted at least 3 professionals before receiving their bipolar diagnosis, and 34% reported that over 10 years elapsed between their first professional contact and the bipolar diagnosis. A more recent DMDA survey of 600 patients with bipolar disorder in the year 2000[18] found similar results, with 69% of patients reporting that they had initially been misdiagnosed.

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Smaller studies involving bipolar patients in clinical practice settings have also found high rates of misdiagnosis, ranging from roughly 25% to 50%.[19–22]

In both DMDA surveys, the most common incorrect diagnosis received by patients with bipolar disorder was unipolar depression,[17,18] which may be partly because the first episode of mood disturbance is frequently depressive rather than manic.[23] Any misdiagnosis of bipolar disorder may have negative consequences for patients because it could delay delivery of treatments known to be effective for bipolar disorder. However, a misdiagnosis of depression carries added risk because antidepressants, when administered without concurrent mood stabilizers, can induce hypomania or mania in many bipolar patients.[21,24–27]

Two recent studies[28,29] used claims data to examine unrecognized and recognized bipolar disorder among patients treated with antidepressants. Findings indicated that unrecognized bipolar disorder was associated with increased overall direct and indirect costs[28,29] as well as higher hospitalization and suicide rates.[29] While these studies highlight the substantial personal and economic costs of misdiagnosis, the data only represent misdiagnosed bipolar patients who are receiving antidepressants. These previous results do not provide insight into treatment patterns and costs among a general sample of misdiagnosed bipolar patients. Thus, the current study builds on this previous work by identifying and examining a sample of bipolar patients misdiagnosed with depression, regardless of treatment received.

In the current analyses, bipolar patients misdiagnosed with depression in 2000 were compared with correctly diagnosed bipolar patients, correctly diagnosed patients with depression, and individuals without a psychiatric disorder. Data from the year 2001 were used to assess whether the diagnosis in 2000 would be considered a correct diagnosis or a misdiagnosis. The first goal of the analyses was to compare the psychiatric and medical comorbidities of these cohorts in order to better characterize bipolar patients who are misdiagnosed. The second goal was to examine service utilization and psychopharmacologic treatment patterns among these patients in order to assess the impact of misdiagnosis on delivery of appropriate services and treatment. Finally, costs of these services and treatments were analyzed in order to assess the economic cost of misdiagnosis.

METHOD

Data Source

This study is a retrospective analysis of data from the MarketScan Commercial Claims and Encounters (CCE) database (MEDSTAT, Ann Arbor, Mich.), which provides information for the study of trends in health care cost, utilization, and treatment patterns. This database captures the health care experience of over 3 million individuals in each of the 2 years relevant to the current study (2000 and 2001). The database incorporates data from over 40 large employers on insurance plan enrollment and medical/prescription claims pertaining to both inpatient and outpatient services. Each medical service claim includes 1 or more *International Classification of Diseases*, 9th Edition, Clinical Modification (ICD-9-CM) diagnostic codes characterizing the patient's clinical status. Individuals in the database include current employees and retirees with Medicare supplemental insurance, as well as spouses and dependents of the primary insured. This database has been analyzed and described in numerous published studies.[30–32]

Sample Selection

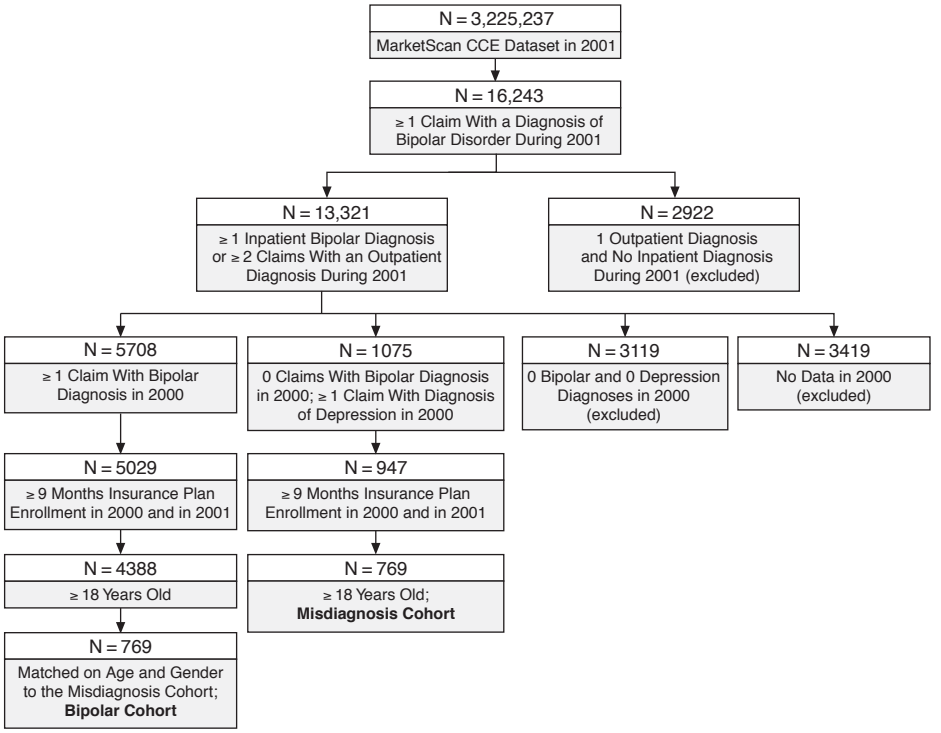
In order to identify misdiagnosed and correctly diagnosed patients with bipolar disorder, ICD-9-CM codes from 2000 and 2001 were examined (see Figure 1 for a summary of sample selection procedures). First, from the full 2001 database, 16,243 individuals with insurance claims indicating a diagnosis of bipolar disorder were selected based on ICD-9-CM codes (296.0, 296.1, 296.4 to 296.8). Patients who had only a single outpatient claim with a bipolar diagnosis (N = 2922) were excluded from the analyses in order to ensure reasonable accuracy of the bipolar diagnosis in the year 2001. Another 13,321 individuals had at least 1 inpatient claim or 2 outpatient claims with a diagnosis of bipolar disorder.

Among the 13,321 remaining bipolar patients, diagnoses during the year 2000 were examined. Patients were considered to have been misdiagnosed with depression in 2000 if they had no claims with a diagnosis of bipolar disorder, but had at least 1 claim with a diagnosis of depression as indicated by ICD-9-CM codes 296.2 or 296.3 (N = 1075). To be included in the analyses, these 1075 misdiagnosed patients had to meet 2 additional criteria: (1) age of at least 18 years and (2) insurance plan enrollment for at least 9 months in each year (2000 and 2001) to ensure that sufficient medical claims data would be available. After applying these 2 criteria, the "misdiagnosis cohort" consisted of 769 patients diagnosed with bipolar disorder in 2001 and misdiagnosed with unipolar depression in 2000.

Of the 13,321 bipolar patients in year 2001, 5708 individuals also had a bipolar diagnosis in the year 2000, and these were considered to be accurately diagnosed in 2000. After applying the age and enrollment criteria described above, 4388 bipolar patients remained. Finally, 769 bipolar patients were selected for the "bipolar cohort" based on age and gender matching to the misdiagnosis cohort.

Two additional comparison groups were identified. The following criteria were used to select patients for a depression comparison group: (1) at least 1 inpatient claim or 2 outpatient claims with a diagnosis of depression in 2001, (2) at least 1 inpatient claim or 2 outpatient claims with a diagnosis of depression in 2000, and (3) no diagnoses of

Figure 1. Selection of Misdiagnosed Bipolar and Recognized Bipolar Cohorts



Abbreviation: CCE = Commercial Claims and Encounters.

bipolar disorder in either 2000 or 2001. A total of 20,214 individuals met these criteria, and 16,710 of these patients also met age (≥ 18 years) and enrollment criteria (≥ 9 months insurance plan coverage in 2000 and in 2001). A "depression cohort" of 769 individuals was selected from the group of 16,710 patients by matching on age and gender to the misdiagnosis cohort.

Finally, a "no psychiatric disorders" cohort of 769 individuals was selected from the general CCE sample based on the following criteria: meeting age and enrollment criteria described above, having no claims with a diagnosis of any psychiatric disorder (ICD-9-CM codes 290 to 319) in either 2000 or 2001, and matching on age and gender to the misdiagnosis cohort. In sum, sample selection resulted in 4 age- and gender-matched cohorts of equal sizes: (1) a misdiagnosis cohort, (2) a bipolar cohort, (3) a depression cohort, and (4) a cohort with no psychiatric disorders.

Statistical Procedures

Analyses were conducted to compare the misdiagnosis cohort to the 3 matched comparison cohorts (bipolar, depression, and no psychiatric disorders) during the year 2000, which was the year of misdiagnosis. Separate sets of logistic regressions were used to examine potential cohort differences with regard to dichotomous dependent variables (coded as 1 if present and 0 if absent). These dependent variables included psychiatric comorbidities, medical comorbidities, service utilization, and psychopharmacologic treatment patterns. The psychiatric and medical comorbidities were identified based on ICD-9-CM codes as listed on inpatient and outpatient insurance claims in 2000. Medical conditions were grouped according to the comorbidity algorithm developed by Elixhauser et al.[33] Psychopharmacologic treatment was analyzed based on the following drug categories: anticonvulsants (most commonly divalproex sodium, gabapentin, carbamazepine, topiramate, lamotrigine), lithium, antipsychotics (most commonly olanzapine, risperidone, quetiapine), antidepressants (most commonly fluoxetine, venlafaxine, bupropion, sertraline), benzodiazepines (most commonly clonazepam, alprazolam, lorazepam), and anxiolytics/sedatives/hypnotics (most commonly zolpidem, buspirone).

Each logistic regression model included a dichotomous diagnostic cohort variable as a predictor, coded as 1 for the misdiagnosis cohort and 0 for the comparison cohort (i.e., bipolar, depression, or no disorders). To select covariates, indications of model fit (e.g., c-index and the Hosmer and Lemeshow test) were examined for several models conducted with various combinations of covariates. Based on these exploratory analyses, age, gender, and insurance plan

Table 1. Demographic Characteristics of the 4 Age- and Gender-Matched Study Cohorts

Characteristic	Bipolar, Recognized (N = 769)[a]	Bipolar, Misdiagnosed (N = 769)[b]	Depression (N = 769)[c]	No Psychiatric Disorders (N = 769)[d]
Gender, N (%)				
Male	246 (32.0)	246 (32.0)	246 (32.0)	246 (32.0)
Female	523 (68.0)	523 (68.0)	523 (68.0)	523 (68.0)
Age, mean (SD), y	42.4 (11.3)	42.3 (11.3)	42.8 (10.6)	42.7 (11.0)

[a]Diagnosed with bipolar disorder in 2000 and 2001.
[b]Diagnosed with bipolar disorder in 2001, but misdiagnosed with depression in 2000.
[c]Diagnosed with depression in 2000 and 2001.
[d]No psychiatric disorders in either 2000 or 2001.

Table 2. Comparisons of Psychiatric Comorbidity: Misdiagnosed Bipolar vs. Recognized Bipolar and Depression[a]

Comorbid Psychiatric Disorder (ICD-9-CM codes)	Bipolar, Recognized (N = 769), %[b]	Bipolar, Misdiagnosed (N = 769), %[c]	Depression (N = 769), %[d]	Misdiagnosed Bipolar vs Recognized Bipolar		Misdiagnosed Bipolar vs Depression	
				OR[e]	95% CI	OR[e]	95% CI
Generalized anxiety disorder	1.1	2.1	1.4	2.0*	1.1 to 3.6	1.6	0.9 to 2.8
Panic disorder	1.1	2.1	1.5	2.0*	1.1 to 3.6	1.4	0.8 to 2.5
Phobic disorder	0.7	1.0	0.8	1.6	0.7 to 3.6	1.2	0.6 to 2.6
Obsessive-compulsive disorder	1.1	1.4	0.5	1.2	0.6 to 2.3	3.0*	1.3 to 7.2
Personality disorder	2.3	1.8	0.8	0.7	0.4 to 1.2	2.1*	1.1 to 4.1
Antisocial personality disorder	0.1	0.1	0.0	1.0	0.1 to 15.6	…[f]	…
Sexual deviations and disorders	0.3	0.3	0.3	1.2	0.3 to 4.6	1.2	0.3 to 4.6
Alcohol abuse[g]	2.1	2.3	1.1	1.1	0.7 to 1.8	2.2*	1.2 to 3.9
Drug abuse[g]	1.9	2.3	0.8	1.2	0.7 to 2.0	2.9**	1.5 to 5.4
Psychotic disorder[g]	8.6	6.8	3.3	0.8*	0.6 to 1.0	2.3***	1.6 to 3.2

[a]Percentages indicate the proportion of each cohort that was diagnosed with the comorbid psychiatric disorder in the year 2000.
[b]Diagnosed with bipolar disorder in 2000 and 2001.
[c]Diagnosed with bipolar disorder in 2001, but misdiagnosed with depression in 2000.
[d]Diagnosed with depression in 2000 and 2001.
[e]Odds ratios and 95% confidence intervals obtained from logistic regression equations, 1 for each of the potentially comorbid disorders (coded as 1 if present, 0 if absent), while controlling for age, gender, and insurance plan type. Each equation contained a cohort variable as a predictor (coded as 1 for misdiagnosis, 0 for the other cohort). Asterisks indicate that odds of having the comorbid disorder were significantly different between the 2 cohorts being compared at *p < .05, **p < .01, and ***p < .001.
[f]An odds ratio could not be computed, because there were no patients in the depression group who had antisocial personality disorder.
[g]Alcohol and drug abuse codes based on algorithm presented by Elixhauser et al.[33] Alcohol abuse: 291.1, 291.2, 291.5, 291.8, 291.9, 303.90–303.93, 305.00–305.03, V113. Psychotic disorders identified using any code beginning with 295 (schizophrenic disorders) or any code beginning with 296 and having a fifth digit of 4, which indicates "severe, specified as with psychotic behavior" (e.g., 296.04).

type (4-level categorical variable: comprehensive, preferred provider organization [PPO], health maintenance organization [HMO], point of service with capitation) were selected to be covariates in all logistic regression models. Odds ratios, 95% confidence intervals, and statistical significance levels are presented.

Analysis of variance (ANOVA) models were used to compare the cohorts with respect to continuous cost variables, reflecting cost of treatment in the year 2000. Costs of psychopharmacologic drug treatments are summarized and reported in terms of ingredient cost plus dispensing fee. Treatment costs are presented in terms of gross payments. Because the cohort with no psychiatric disorders had virtually no psychiatric treatment costs, this cohort was excluded from these ANOVAs. Thus, the ANOVAs include a 3-level diagnostic variable (misdiagnosis, bipolar, depression). For models with a statistically significant overall F value, Scheffe's post hoc pairwise comparisons between group means were conducted. Results of all analyses were considered statistically significant at a level of $p < .05$, and all significance tests were 2-tailed.

RESULTS

Demographics

After sample selection and matching procedures were completed, the 4 study cohorts each consisted of 769 patients (see Table 1 for demographics). Each cohort included 523 women (68.0%) and 246 men (32.0%). The misdiagnosis cohort had a mean age of 42.3 years. Because the 3 comparison cohorts were matched to the misdiagnosis cohort with regard to age, the mean ages of the bipolar, depression, and no psychiatric disorders cohorts were very similar to the misdiagnosis cohort.

Psychiatric Comorbidities

In comparisons between the misdiagnosis cohort and the depression cohort, all reported odds ratios were greater than 1, suggesting that unrecognized bipolar disorder was associated with higher overall rates of psychiatric comorbidity than depression (Table 2). Specifically, the misdiagnosis cohort had significantly greater odds of being diagnosed with obsessive-compulsive

Table 3. Comparisons of Medical Comorbidity: Misdiagnosed Bipolar vs. Recognized Bipolar and Depression[a,b]

Comorbid Medical Conditions	Bipolar, Recognized (N = 769), %[c]	Bipolar, Misdiagnosed (N = 769), %[d]	Depression (N = 769), %[e]	No Psychiatric Disorders (N = 769),%[f]
Congestive heart failure	0.5	0.3	0.8	0.2
Cardiac arrhythmias	1.4	1.5	1.8	0.5**
Pulmonary circulation disorders	0.1	0.1	0.3	0.0
Peripheral vascular disorders	0.5	0.4	0.7	0.1
Hypertension	9.6	8.9	8.1	7.0*
Neurologic disorders	3.2	2.9	1.4**	0.3***
Chronic pulmonary disease	6.8	7.2	6.8	3.6
Diabetes (uncomplicated)	4.1	4.0	3.2	2.5
Diabetes (complicated)	0.7	1.0	0.8	0.6
Hypothyroidism	6.1	4.7	3.4	2.5***
Peptic ulcer disease	0.3	0.5	0.1	0.2
AIDS	0.0	0.1	0.1	0.1
Weight loss	0.0	0.1	0.1	0.0
Fluid and electrolyte disorders	1.6	1.8	1.6	0.1***

[a]All comorbidities based on algorithm presented by Elixhauser et al.[33]
[b]Percentages indicate the proportion of each cohort that was diagnosed with the comorbid medical condition in the year 2000. Asterisks indicate that odds of having the comorbid condition were significantly greater for the misdiagnosis cohort than for the other cohort (at *p < .05, **p < .01, and ***p < .001), as indicated by logistic regression equations, 1 for each of the potentially comorbid conditions (coded as 1 if present, 0 if absent). Each equation contained a cohort variable as a predictor (coded as 1 for misdiagnosis, 0 for the other cohort), while controlling for age, gender, and insurance plan type.
[c]Diagnosed with bipolar disorder in 2000 and 2001.
[d]Diagnosed with bipolar disorder in 2001, but misdiagnosed with depression in 2000.
[e]Diagnosed with depression in 2000 and 2001.
[f]No psychiatric disorders in either 2000 or 2001.
Abbreviation: AIDS = acquired immunodeficiency syndrome.

disorder (1.4% vs. 0.5%), a personality disorder (1.8% vs. 0.8%), alcohol abuse (2.3% vs. 1.1%), drug abuse (2.3% vs. 0.8%), or a psychotic disorder (6.8% vs. 3.3%). The 2 cohorts did not differ significantly in odds of having generalized anxiety disorder, panic disorder, or a phobia.

There were also significant differences in psychiatric comorbidity rates between the misdiagnosis cohort and the recognized bipolar cohort (Table 2). Specifically, the misdiagnosis cohort had significantly greater odds of being diagnosed with generalized anxiety disorder (2.1% vs. 1.1%) and panic disorder (2.1% vs. 1.1%), whereas the bipolar cohort had significantly greater odds of being diagnosed with a psychotic disorder (6.8% vs. 8.6%). The 2 cohorts had similar rates of other psychiatric disorders, such as personality disorders, alcohol abuse, and drug abuse. Like the depression cohort, both the recognized and misdiagnosed bipolar cohorts had very low rates of antisocial personality disorder and sexual deviations/disorders.

Medical Comorbidities

The most common medical conditions among the misdiagnosis cohort were hypertension (8.9%), chronic pulmonary disease (7.2%), hypothyroidism (4.7%), and uncomplicated diabetes (4.0%) (Table 3). The misdiagnosed bipolar patients had higher rates of most medical conditions compared with the control group of individuals without a psychiatric disorder. These differences were statistically significant for cardiac arrhythmias, hypertension, neurologic disorders, hypothyroidism, and fluid/electrolyte disorders. In contrast, there were no statistically significant differences between the misdiagnosed bipolar and recognized bipolar cohorts in rates of any medical comorbidities. The only significant difference between the misdiagnosis cohort and the depression cohort was in rates of neurologic disorders, which were significantly more prevalent among the misdiagnosis cohort (2.9% vs. 1.4%).

Rates of Service Utilization

The misdiagnosed bipolar, recognized bipolar, and depression cohorts all had moderate rates of psychiatric service utilization during the year 2000 (Table 4). Over 40% of each of the 3 cohorts had received some psychiatric service, and over 25% of each cohort had seen a psychiatrist during the year 2000. A relatively small percentage of patients had seen a psychologist (10.5% misdiagnosis; 8.5% bipolar; 9.7% depression), and very few of the patients had received substance abuse services (≤ 1.0% of each cohort). The misdiagnosis cohort had significantly greater rates of hospital emergency room visits than the depression cohort (9.6% vs. 7.3%) and significantly greater rates of hospital admissions for medical reasons compared with the bipolar cohort (4.4% vs. 2.6%). However, a greater percentage of patients in the depression cohort had received any psychiatric service compared with the misdiagnosis cohort (43.4% vs. 40.9%).

Rates of Psychopharmacologic Treatment

Logistic regressions revealed that the misdiagnosis cohort differed in psychopharmacologic treatment patterns compared with both the bipolar cohort and the depression cohort (Table 4). Compared with the bipolar cohort, the

Table 4. Comparison of Service Utilization and Psychopharmacologic Treatment: Misdiagnosed Bipolar vs. Recognized Bipolar and Depression [a]

Treatment	Bipolar, Recognized (N = 769), %[b]	Bipolar, Misdiagnosed (N = 769), %[c]	Depression (N = 769), %[d]	Misdiagnosed Bipolar vs Recognized Bipolar OR[e]	Misdiagnosed Bipolar vs Recognized Bipolar 95% CI	Misdiagnosed Bipolar vs Depression OR[e]	Misdiagnosed Bipolar vs Depression 95% CI
Psychiatric and medical services							
Hospital emergency room visit	10.2	9.6	7.3	0.9	0.7 to 1.2	1.4*	1.1 to 1.9
Hospital admission for psychiatric reasons or substance abuse	7.8	7.0	2.7	0.9	0.7 to 1.2	2.8***	1.9 to 4.1
Hospital admission for medical reasons	2.6	4.4	3.2	1.7**	1.2 to 2.6	1.4	0.9 to 2.0
Seen a psychiatrist	29.0	26.8	26.2	0.8	0.7 to 1.0	1.0	0.9 to 1.3
Seen a psychologist	8.5	10.5	9.7	1.3	1.0 to 1.7	1.1	0.8 to 1.4
Received substance abuse services	1.0	0.8	0.3	0.9	0.4 to 2.0	2.7	1.0 to 7.6
Received any psychiatric services	40.4	40.9	43.4	1.1	0.9 to 1.5	0.7*	0.5 to 1.0
Drug treatment							
Anticonvulsants	26.8	15.3	7.3	0.4***	0.3 to 0.5	2.6***	2.0 to 3.3
Antidepressants	31.6	38.7	39.2	2.1***	1.6 to 2.6	0.9	0.7 to 1.2
Anxiolytic/sedative/hypnotic	9.5	13.2	10.1	1.5***	1.2 to 1.9	1.4**	1.1 to 1.8
Antipsychotics	17.8	11.4	5.5	0.5***	0.4 to 0.7	2.4***	1.8 to 3.2
Lithium	15.2	5.9	1.3	0.3***	0.2 to 0.4	5.1***	3.1 to 8.4
Benzodiazepines	20.2	22.3	18.8	1.2	1.0 to 1.5	1.4**	1.1 to 1.7

[a]Percentages indicate the proportion of each cohort receiving each type of service or treatment at any point during the year 2000.
[b]Diagnosed with bipolar disorder in 2000 and 2001.
[c]Diagnosed with bipolar disorder in 2001, but misdiagnosed with depression in 2000.
[d]Diagnosed with depression in 2000 and 2001.
[e]Odds ratios and 95% confidence intervals obtained from logistic regression equations, 1 for each of the services or treatments (coded as 1 if present, 0 if absent). Each equation contained a cohort variable as a predictor (coded as 1 for misdiagnosis, 0 for the other cohort), while controlling for age, gender, and insurance plan type. Asterisks indicate that odds of having the comorbid disorder were significantly different between the 2 cohorts being compared at *p < .05, **p < .01, and ***p < .001.

misdiagnosis cohort had significantly greater odds of receiving antidepressants (38.7% vs. 31.6%) and anxiolytics (13.2% vs. 9.5%). However, the bipolar cohort had comparatively greater odds of receiving anticonvulsants (26.8% vs. 15.3%), antipsychotics (17.8% vs. 11.4%), and lithium (15.2% vs. 5.9%). Compared with the depression cohort, the misdiagnosis cohort had significantly greater odds of receiving anticonvulsants (15.3% vs. 7.3%), anxiolytics (13.2% vs. 10.1%), antipsychotics (11.4% vs. 5.5%), lithium (5.9% vs. 1.3%), and benzodiazepines (22.3% vs. 18.8%). The misdiagnosis and depression cohorts were not significantly different in odds of receiving antidepressants.

Cost of Service Utilization

Analysis of variance models with Scheffe's post hoc comparisons revealed few statistically significant group differences in costs of psychiatric and medical services (Table 5). Compared with the depression cohort, the misdiagnosis cohort had significantly higher costs related to hospital admissions for psychiatric reasons or substance abuse ($1125.7 vs. $416.5). In addition, the bipolar cohort had significantly greater costs than the depression cohort for treatment from a psychiatrist ($417.3 vs. $293.5) and hospital admissions for psychiatric reasons or substance abuse ($1426.3 vs. $416.5). Otherwise, there were no significant differences between these 3 cohorts in gross payments for psychiatric and medical services.

Cost of Psychopharmacologic Treatment

There were substantial cohort differences in costs of various psychopharmacologic treatments (Table 5). All 3 cohorts were significantly different from each other with respect to costs of anticonvulsants, antipsychotics, and lithium. For each of these 3 drugs, the bipolar cohort was associated with the highest cost, the misdiagnosis cohort had the next greatest cost, and the depression cohort had the least cost. For anticonvulsants, antipsychotics, and lithium, patients in the bipolar cohort had mean costs of $442.2, $309.9, and $67.0, respectively. In comparison, the misdiagnosis cohort had mean costs of $221.0, $185.0, and $19.9, respectively, while the depression cohort had costs of $69.9, $74.3, and $5.3, respectively.

With regard to antidepressants, both the misdiagnosis cohort ($703.9) and the depression cohort ($657.0) had statistically significantly greater mean costs than the bipolar cohort ($497.1). However, the misdiagnosis and depression cohorts were not significantly different from each other. Both the misdiagnosis cohort ($1319.9) and the bipolar cohort ($1476.7) had significantly greater overall cost for psychopharmacologic treatment compared with the depression cohort ($950.5), but the misdiagnosis and bipolar cohorts were not significantly different from each other.

Overall Treatment Costs

The misdiagnosis cohort had significantly higher overall annual treatment costs than the depression co-

Table 5. Direct Treatment Costs in the Year 2000

Treatment	Bipolar, Recognized (N = 769)[a]	Bipolar, Misdiagnosed (N = 769)[b]	Depression (N = 769)[c]	Overall F Value	Pairwise Comparison p Values[d]		
					Misdiagnosis vs Bipolar	Bipolar vs Depression	Misdiagnosis vs Depression
Gross payments for psychiatric and medical services, mean (SD), $							
Hospital emergency room visit	126.6 (700.7)	160.6 (608.6)	102.4 (439.1)	1.9			
Hospital admission for psychiatric reasons or substance abuse	1426.3 (5081.0)	1125.7 (4379.7)	416.5 (3587.1)	10.7***		p < .001	p < .01
Hospital admission for medical reasons	405.2 (3451.7)	657.2 (3309.1)	543.8 (3825.1)	1.0			
Seen a psychiatrist	417.3 (770.0)	363.0 (835.4)	293.5 (657.3)	5.2**		p < .01	
Seen a psychologist	216.9 (788.2)	197.4 (610.7)	220.5 (659.4)	0.3			
Received substance abuse services	11.0 (123.2)	15.8 (168.7)	2.9 (40.7)	2.2			
Any psychiatric service	1149.6 (1885.3)	1017.1 (1567.4)	1032.7 (1383.3)	1.5			
Drug treatment: ingredient cost plus dispensing fee, mean (SD), $							
Anticonvulsants	442.2 (715.6)	221.0 (546.3)	69.9 (297.5)	90.0***	p < .001	p < .001	p < .001
Antidepressants	497.1 (674.2)	703.9 (847.7)	657.0 (717.5)	16.1***	p < .001	p < .001	
Anxiolytic/sedative/hypnotic	65.7 (254.2)	96.8 (307.8)	70.9 (258.0)	2.8			
Antipsychotics	309.9 (769.8)	185.0 (583.7)	74.3 (400.2)	29.3***	p < .001	p < .001	p < .01
Lithium	67.0 (146.9)	19.9 (77.6)	5.3 (42.5)	81.4***	p < .001	p < .001	p < .05
Benzodiazepines	94.9 (230.4)	93.3 (226.6)	73.0 (190.7)	2.4			
Total psychopharmacologic treatment[e]	1476.7 (1624.8)	1319.9 (1545.3)	950.5 (1144.8)	26.6***		p < .001	p < .001
Total treatment costs, mean (SD), $[e]							
Inpatient	1794.4 (6407.2)	1701.9 (5489.2)	1146.0 (5060.9)	2.9			
Outpatient	4359.1 (6550.5)	4705.0 (5919.8)	4072.3 (6513.4)	1.9			
Inpatient + outpatient	6153.5 (10,301.9)	6406.7 (8890.8)	5218.3 (9876.9)	3.2*			
Drug	2446.6 (2955.2)	2354.5 (2587.7)	2069.9 (2612.9)	4.0*		p < .05	
Inpatient + outpatient + drug	8600.0 (11,258.9)	8761.4 (9774.0)	7288.2 (10,859.6)	4.4*			p < .05

[a]Diagnosed with bipolar disorder in 2000 and 2001.
[b]Diagnosed with bipolar disorder in 2001, but misdiagnosed with depression in 2000.
[c]Diagnosed with depression in 2000 and 2001.
[d]For models with a statistically significant overall F value, Scheffe's post hoc pairwise comparisons between group means were conducted.
[e]Total psychopharmacologic treatment costs are the sum of costs for anticonvulsants, antidepressants, anxiolytics/sedatives/hypnotics, antipsychotics, lithium, and benzodiazepines. All other totals were computed based on all costs in the inpatient, outpatient, and drug files of the MarketScan Commercial Claims and Encounters (CCE) database.
*p < .05; **p < .01; ***p < .001.

hort, as indicated by the sum of inpatient + outpatient + drug costs ($8761.4 vs. $7288.2) (Table 5). Compared with the depression cohort, the misdiagnosis cohort also had numerically higher costs for each of the 3 individual cost components (i.e., inpatient, outpatient, drug), but these group differences were not statistically significant. The bipolar cohort had significantly greater drug costs than the depression cohort ($2446.6 vs. $2069.9). Although the misdiagnosis cohort had numerically greater overall treatment costs than the bipolar cohort ($8761.4 vs. $8600.0), this difference was not statistically significant.

DISCUSSION

Misdiagnosis is often said to present a great risk to patients with bipolar disorder because misdiagnosed patients are not likely to receive effective pharmacologic treatment.[1,34,35] Current findings provide compelling support for this hypothesis, indicating that misdiagnosis is associated with ineffective pharmacologic treatment patterns. Compared with correctly diagnosed bipolar patients, misdiagnosed patients in the current sample were significantly less likely to receive the medications that current guidelines recommend as first-line treatments for manic and depressive episodes of bipolar disorder, including anticonvulsants, antipsychotics, and lithium.[13]

In addition, antidepressant use was significantly more common among misdiagnosed bipolar patients than among correctly diagnosed bipolar patients. For bipolar patients, antidepressants are not recommended as monotherapy because these medications may induce mania, hypomania, or rapid cycling.[1,21,24,27,36–38] Some researchers have expressed concerns regarding antidepressants even as adjunct treatment to medications such as lithium or valproate because they may actually cause more mood episodes to occur over long-term treatment.[25] In sum, the treatment patterns identified in the current analysis indicate that misdiagnosed bipolar patients tend to receive inappropriate treatment, involving overuse of antidepressants and underuse of potentially effective medications.

These treatment patterns were also reflected in the analyses of treatment-related costs. Previous studies conducted among bipolar patients receiving antidepressants have found that misdiagnosis of bipolar patients is associated with high overall treatment costs.[28,29] Current analyses of total inpatient, outpatient, and pharmacologic treatment costs revealed similar results. The present results also add to prior findings by suggesting that these substantial economic resources are frequently spent on ineff-

fective, possibly harmful, treatment regimens. In the long term, these patients may be expected to incur greater direct treatment costs until they receive a correct diagnosis, which would lead to more effective treatment. Furthermore, the inadequate treatment associated with misdiagnosis may also lead to increased indirect costs that are known to be associated with bipolar disorder, such as work loss and decreased productivity.[5,39,40]

Analyses of comorbidity may provide insight into the characteristics of bipolar patients who are misdiagnosed. Compared to patients with unipolar depression, the misdiagnosed patients appear to have greater overall psychiatric comorbidity, particularly obsessive-compulsive disorder, psychosis, and substance abuse. These comorbidities suggest a possible strategy for improving recognition of bipolar disorder among patients who present with depressive symptoms in clinical settings. The patients who present with this pattern of comorbidities may benefit from additional screening for bipolar disorder. Future research is needed to further identify and confirm characteristics that may distinguish bipolar patients from unipolar patients among individuals with depressive symptoms.

Misdiagnosed bipolar patients also had different comorbidity patterns than correctly diagnosed bipolar patients, in that the misdiagnosed cohorts had significantly higher rates of anxiety disorders. The increased anxiety could be partly caused by the misdiagnosis itself. Previous research on bipolar disorder has found misdiagnosis to be associated with elevated suicide and hospitalization rates.[29] It is possible that the inadequate treatment associated with misdiagnosis contributes to anxiety as well as these other risks. Research with longer-term longitudinal study designs may determine whether there are causal relationships between misdiagnosis and these negative outcomes.

In contrast to analyses of psychiatric comorbidity, analyses of medical comorbidity revealed minimal differences between the 3 psychiatric cohorts. All 3 cohorts had higher rates of medical comorbidities compared to individuals without a psychiatric diagnosis, particularly cardiac arrhythmias, neurological disorders, hypothyroidism, and fluid/electrolyte disorders. However, present results do not indicate that medical comorbidities can be used to differentiate misdiagnosed from correctly diagnosed bipolar patients.

In the current study, the 8% rate of misdiagnosis (i.e., 1075 misdiagnosed patients out of 13,321 total bipolar patients; see Figure 1) may initially appear somewhat low in comparison to the higher rates of misdiagnosis reported in previous studies.[17,18] However, the current study's misdiagnosis rate is not comparable to rates in these previous studies. The percentage in the current study refers only to patients diagnosed with bipolar disorder in the year 2001 and misdiagnosed with depression during the year 2000. Therefore, this percentage does not represent the rate of overall misdiagnosis, which is likely to be much higher than 8%. For example, it is probable that other bipolar patients were misdiagnosed in 2000 with psychiatric disorders other than depression. Furthermore, other patients may not have received any diagnosis during 2000, but may have been misdiagnosed during previous years. In sum, this study only identified patients who received 1 type of misdiagnosis during a 1-year period, and the current analyses were not designed to identify overall rates of misdiagnosis.

As with any study using claims data, there are several limitations of the current analysis. Several important demographic characteristics are unavailable in the MarketScan CCE dataset, including ethnicity, marital status, employment status, and socioeconomic status. For a study of misdiagnosis, ethnicity may be especially important in light of long-standing questions regarding the interaction between racial background and diagnosis of severe psychopathology.[41–44] Other potentially important unavailable information includes the diagnostic distinction between bipolar I and bipolar II. Given that the hypomanic symptoms of bipolar II may be more difficult to recognize than the manic symptoms of bipolar I, it could be hypothesized that bipolar II patients are overrepresented in the misdiagnosis cohort. It is hoped that future research will examine the role of ethnicity and bipolar subtype in misdiagnosis.

Confidence in the results is also limited by the degree of diagnostic certainty. Since the current study used claims data, it was not possible to obtain clinical confirmation of diagnoses. Efforts were made to ensure the accuracy of diagnoses in the year 2001 by requiring either 2 outpatient diagnoses or 1 inpatient diagnosis. This approach was based on the hypothesis that an inpatient diagnosis is most likely to be accurate because symptoms are more pronounced and because clinicians would be able to observe the patient over a longer period of time. Two outpatient diagnoses were required because it was assumed that patients receiving bipolar diagnoses at 2 points in time were more likely to be correctly diagnosed. Despite these efforts, it is not possible to be absolutely certain that all patients were categorized into the correct diagnostic cohort when using claims data.

Overall, current results strongly suggest that misdiagnosis presents a costly barrier to effective treatment of patients with bipolar disorder. Consequently, it is recommended that steps be taken to minimize the chance of misdiagnosis in clinical settings whenever possible. Strategies for avoiding misdiagnosis among bipolar patients with depressive symptoms have been suggested, including asking patients about a history of mania/hypomania, asking about a family history of bipolar disorder, and involving family members in the evaluation process.[35] In addition, administration of a brief screening instrument, such as the Mood Disorder Questionnaire, may efficiently

improve recognition of bipolar disorder.[13,45] By taking these steps, clinicians may be able to reduce rates of misdiagnosis and effectively treat more patients with bipolar disorder.

Drug names: alprazolam (Xanax and others), bupropion (Wellbutrin and others), buspirone (Buspar and others), carbamazepine (Carbatrol, Tegretol, and others), clonazepam (Klonopin and others), divalproex sodium (Depakote), fluoxetine (Prozac and others), gabapentin (Neurontin), lamotrigine (Lamictal), lithium (Lithobid, Eskalith, and others), lorazepam (Ativan and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft), topiramate (Topamax), venlafaxine (Effexor), zolpidem (Ambien).

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