Diagnosis of Unipolar Depression Following Initial Identification of Bipolar Disorder: A Common and Costly Misdiagnosis

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Background: Bipolar disorder is challenging to diagnose in medical practice.

Objectives: Our objectives were (1) to determine the rate of depression misdiagnosis in patients previously diagnosed with bipolar disorder in administrative claims, (2) to determine the resulting increased treatment costs, and (3) to verify the misdiagnoses in the medical charts for a subset of patients.

Method: We employed cohort analysis using claims from a large, commercial, U.S. health plan from January 2001 through December 2003. Inclusion criteria included 2 bipolar disorder diagnoses (ICD-9-CM criteria), continuous enrollment for 1 year before and after initial bipolar disorder diagnosis, age 18–64 years, and a pharmacy benefit. Propensity scoring was used to control for differences between patients with and without 2 depression diagnosis. Medical charts were obtained for 100 patients, including 76 with a bipolar disorder diagnosis chart from a second provider.

Results: Of 3119 bipolar disorder patients meeting inclusion criteria, 857 (27.5%) had subsequent depression misdiagnoses during the follow-up year. These patients had 1.82 times more psychiatric hospitalizations and 2.47 times more psychiatric emergency room visits. For 673 patients (78.5%), a different provider gave the depression misdiagnosis. Annual per-patient treatment costs were significantly higher (p < .001) for those diagnosed with depression (\$12,594) than for those not (\$9405). In the chart review, both the bipolar disorder and subsequent depression diagnoses were confirmed for 65.8% (50/76) of the patients who had charts from 2 different providers.

Conclusions: More than one quarter of individuals diagnosed with bipolar disorder received an ostensible depression misdiagnosis during the follow-up period. Significant (p = .001) increases in psychiatric inpatient hospitalization suggest that improvements in the continuity of care could improve outcomes and reduce costs. (J Clin Psychiatry 2008;69:749–758)

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B ipolar disorder, a severe and recurrent mental disorder, is characterized by episodes of elated mood and of depressed mood. Prevalence of this disorder is difficult to ascertain and varies by setting and target population. Epidemiologic studies have reported lifetime prevalences ranging from 0.2% to 5.1%, ¹⁻⁴ with the lower estimates specifically for bipolar I disorder. However, in primary care clinics for low-income individuals, the lifetime prevalence has been reported as high as 9.8%.⁵ In most private insurance claims databases, the prevalence of treated bipolar disorder has been found to be low (0.2%).^{6,7} The low prevalence in administrative claims data can be partially attributed to the fact that only 40% of individuals with bipolar disorder are covered by private insurance⁸ and to the inherent diagnostic challenges of bipolar disorder.

Accurate diagnosis of bipolar disorder is hindered by its episodic nature and its variable symptom presentation. Bipolar I disorder is characterized by full-blown manic episodes and major depressive episodes; bipolar II disorder is characterized by less severe manic episodes (hypomania) and major depressive episodes; and cyclothymia is characterized by episodes of hypomania and less severe depression.⁹ The highly variable symptoms of bipolar disorder, which range from impulsive behavior to fluctuations in energy level, are often attributed to other disorders.⁸ Accurate diagnosis of bipolar disorder requires assessment of symptomatology from a longitudinal rather than a cross-sectional perspective.

Individuals with bipolar disorder are frequently undiagnosed or misdiagnosed in medical practice. Prior to their initial bipolar diagnosis, 69% of individuals with bipolar disorder report being misdiagnosed at least once, most commonly (60%) with unipolar depression. After a misdiagnosis, one third of patients reported that the time to receive a correct diagnosis of bipolar disorder was greater than 10 years.¹⁰

Differential diagnosis from unipolar depression is particularly difficult. An examination of Veterans Affairs claims revealed that 54% of individuals with a bipolar disorder diagnosis were given the differential diagnosis of depression in the same year.¹¹ Part of the challenge of this differential diagnosis lies in the high degree of symptom overlap. When a patient with bipolar disorder experiences a depressive episode, the diagnostic criteria are the same as those for major depressive disorder; the disorders are differentiated on the basis of a history of manic or hypomanic symptoms.9 Unfortunately, patients often do not recall past manic episodes, or do not recall them as problematic,⁸ and, therefore, may not report these past symptoms of mania to clinicians. A substantial proportion of patients who have been previously hospitalized for mania discontinue medication because they do not believe they are ill.¹² Finally, depressive symptoms are present 3 times as often as manic symptoms in patients with bipolar disorder.13

Physicians generally prescribe mood stabilizers for patients with bipolar disorder in order to control mood episodes. Antidepressant monotherapy, the most common treatment for unipolar depression, is contraindicated for patients with bipolar disorder because it can induce mania^{14,15} or accelerate mood cycling.¹⁶ Depressive symptoms of bipolar disorder are less likely to respond to antidepressant monotherapy than to treatment with an antidepressant along with a mood stabilizer.¹⁶ Thus, patients whose bipolar disorder is misdiagnosed as unipolar depression may receive inappropriate treatment that could lead to poor outcomes.

The majority of the literature on diagnostic issues and bipolar disorder has focused on the difficulty of initially recognizing the disorder. The underlying assumption has been that once bipolar disorder is recognized, all future depressive episodes will be recognized as bipolar depression and correctly treated. The objectives of this study were 3-fold: (1) to assess the rate of unipolar depression diagnosis in the year following individuals' initial bipolar diagnosis; (2) to assess the level of increased acute care services (hospitalization and emergency room [ER]) and treatment costs associated with these ostensible depression misdiagnoses, after correcting for background differences; and (3) to verify the misdiagnoses in the medical charts for a subset of the patients.

METHOD

Study Population

This study design used retrospective, longitudinal, administrative claims data from a large, national, managed care organization providing coverage for inpatient care, ambulatory services, and prescription drugs. The study sample was derived from commercially insured health plan members or members with Medicaid managed care coverage, aged 18 to 64 years, who had medical and pharmacy benefits and who were continuously enrolled in the health plan for at least 2 years.

Study patients were required to have had an index bipolar diagnosis between January 1, 2002, and December 31, 2002; continuous enrollment with no bipolar diagnoses in the 12 months prior to the index date (baseline period); and continuous enrollment in the 12 months following the index date (follow-up period). Patients were identified using diagnostic codes for bipolar disorder (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM]: 296.0x, 296.1x, 296.4x, 296.5x, 296.6x, 296.7x, and 296.8x). Patients were required to have had bipolar disorder diagnoses on at least 2 different service dates during the identification period, with no differential diagnosis of schizophrenia (ICD-9-CM: 295.xx) or unipolar depression (ICD-9-CM: 311.xx, 300.4x, 309.1x, 296.2x, 296.3x, or 298.0x) on the same dates of service.

Patients with a diagnosis of unipolar depression on at least 2 separate service dates in the year following the index bipolar disorder diagnosis, with no diagnosis of bipolar disorder on these same service dates, were categorized as having an ostensible depression misdiagnosis (OM). All other patients were considered to have had no depression misdiagnoses (NM).

Measures

Information regarding comorbid conditions present during the study period was obtained from the medical claims database using ICD-9-CM diagnosis and procedure codes. The number of unique claims for specific conditions, including unipolar depression, schizophrenia, anxiety, personality disorder, attention-deficit/ hyperactivity disorder, substance abuse, mental retardation, other mental health diagnoses (all other ICD-9-CM codes between 290.00 and 319.99), and non-mental health diagnoses (all other ICD-9-CM codes), was calculated during the baseline period. In addition, a Charlson Comorbidity Index was constructed as a measure of health status.¹⁷ This assessment, scored 0–33, measures the number and severity of comorbid conditions, with a score of 0 indicating no comorbid conditions.

Medical claims data were used to determine health care utilization, including measures of ambulatory visits (defined using ICD-9-CM codes), visits to an ER, and inpatient hospital visits. Health care utilization was measured in the baseline and follow-up periods for both mental health and non-mental health visits. Mental health visits were identified using ICD-9-CM codes 290.xx-319.xx in the primary diagnosis field on medical claims. Psychotherapy sessions were identified during the baseline period using Current Procedural Terminology (CPT) codes: 90846–90849, 99510, 90853, 90857, 90816– 90822, 90804–90809, 90823–90829, and 90810–90815.

Characteristics of the most recent bipolar diagnosis in the follow-up period were identified and classified by episode type (manic, depressive, mixed, or unspecified), severity (fifth digit of ICD-9-CM code [mild, moderate, severe, psychosis, remission, or unspecified]), place of service (inpatient, ER, or ambulatory), and type of health care professional making the diagnosis (mental health provider, general practitioner [GP], or other). We counted the number of unique mental health providers, GPs, and other providers treating patients during the baseline period, and we identified the type of physician specialty on the first incongruent depression claim in the follow-up period. Health care costs were also calculated during the baseline and follow-up periods. These included total health care costs, mental health and non-mental health ambulatory care costs, inpatient costs, and pharmacy costs.

Pharmacy claims data were used to determine drug utilization and patient adherence to therapy during the study period. We also extracted information regarding the days' supply of filled prescriptions for medications (lithium, antidepressants, anticonvulsants, antipsychotics, and benzodiazepines) during the baseline and follow-up periods.

Chart Review

A chart review was completed for a subset (100) of the patients identified in the claims with potential depression misdiagnoses to confirm that the diagnoses were also in the patient charts. Privacy review board approval was obtained, and, based on information in the claims data, an abstraction firm contacted the providers who initially diagnosed the bipolar disorder. For both the depression and bipolar disorder charts, if a provider was unavailable or was unwilling or unable to allow the chart to be abstracted, then the next provider who gave the relevant diagnosis in the claims data was contacted. Provider selection for chart abstraction was prioritized on the basis of the following hierarchy: hospital/behavioral health facility, psychiatrist with greatest number of visits, psychologist/social worker with greatest number of visits, and other provider with greatest number of visits.

For patients who had been given depression diagnoses by different providers, once a bipolar disorder chart had been abstracted, the abstraction firm contacted the selected provider who had given a depression diagnosis at least 7 days following the index bipolar disorder visit and attempted to abstract that chart. We obtained 24 patient charts in which the same provider had billed with both bipolar disorder and depression diagnoses, and we obtained charts for 76 patients from 2 different providers each, one who had submitted a claim for bipolar disorder and another who had subsequently submitted a unipolar depression claim.

Statistical Methods

A logistic regression model was specified to predict the likelihood of an OM using variables measured in the baseline period. The predicted values (propensity scores) from this analysis were used as covariates in subsequent analyses to control for differences between the 2 cohorts.¹⁸ In order to reduce potential for bias from multicollinearity and endogeneity, we used backward elimination to identify the covariates that were statistically significant in predicting the likelihood of incongruent diagnosis and to reduce the number of insignificant variables in the model specification. The independent variables in the model were measured during the baseline period and are listed in Table 1. The area under the receiver operating characteristic (ROC) curve indicated that the background variables were able to accurately classify a randomly selected OM individual from a randomly selected NM individual 79% of the time.

Poisson and negative binomial regression models were used to investigate the differences in the number of mental health providers, GPs, and other providers in the follow-up period across the 2 cohorts, controlling for baseline covariates, including the number of providers (mental health, GP, other) in the baseline period. We compared differences in medication use from the chart review using the McNemar test.

Two-part models were used to analyze the relationship between depression misdiagnoses and health care costs. These models deal with the unique characteristics of medical expenditure data, which are typically skewed (more variability among patients' expenses when those expenses are large than when they are small—nonconstant variance) and censored (a large number of individuals with no medical expenditures). The first step was to estimate whether individuals had any medical expenditures using logistic regression. In the second step, a generalized linear model (GLM) with a gamma distribution log-link function and robust standard errors was used to estimate positive costs. We combined the results of the 2-part model to predict medical expenses for an individual by multiplying the prediction from each part of the model (the probability of positive expenses multiplied by the predicted medical expense from the GLM specification).¹⁹

RESULTS

Rate and Predictors of Depression Misdiagnosis

A total of 3119 patients diagnosed with bipolar disorder met all inclusion criteria for the analysis (Figure 1). Of

Table 1. Descriptive Statistics: Demographic and Baseline Clinical, Utilization, and Cost Variables by Cohort					
Variable	Ostensible Depression Misdiagnosis (N = 857)	No Depression Misdiagnosis (N = 2262)	Univariate p Value	Propensity Score, p Value	
Demographic variables					
Men, N (%)	266 (31.0)	905 (40.0)	< .001	.028	
Age, mean (SD), y	38.5 (10.8)	38.2 (11.0)	.547		
Region, N (%)					
Northeast	114 (13.3)	238 (10.5)	.029		
South	357 (41.7)	1,008 (44.6)	.144	.056	
West	116 (13.5)	334 (14.8)	.383		
Midwest	270 (31.5)	682 (30.2)	.463		
Plan type, N (%)		. ,			
Commercial	839 (97.9)	2,148 (95.0)	<.001		
Medicaid	18 (2.1)	114 (5.0)	< .001	.003	
Baseline variables					
Baseline unipolar diagnosis indicator, N (%)	519 (60.56)	411 (18.17)	< .001	<.001	
No. of unipolar diagnoses ^a	7.52 (10.61)	1.37 (4.13)	<.001	<.001	
Total cost. \$ ^a	8.453.70 (12.054.26)	6.107.25 (22.306.17)	<.001		
MH ambulatory cost, \$ ^a	947.29 (2.001.71)	334.54 (1.236.56)	<.001		
Non-MH ambulatory cost. \$ ^a	2,502,33 (4,701.62)	1.779.77 (3.932.77)	<.001		
MH emergency room cost, \$ ^a	52.24 (251.39)	37.84 (312.88)	.183		
Non-MH emergency room cost. \$ ^a	218.48 (684.55)	208.06 (945.23)	.734		
MH inpatient cost. \$ ^a	897.70 (3.614.63)	345.12 (1.901.45)	<.001		
Non-MH inpatient cost. \$ ^a	1.133.77 (6.814.27)	1.577.39 (20.608.99)	.367		
MH medication cost. \$ ^a	1.079.08 (1.423.75)	682.18 (1.118.85)	< .001	.007	
Total medication cost. \$ ^a	2.241.15 (3.873.22)	1,527,32 (2,225,40)	<.001		
No. of psychotherapy sessions ^a	6.68 (10.63)	2.10 (6.12)	<.001		
Antidepressant, days' supply ^a	201.24 (197.68)	124.88 (169.65)	< .001		
Lithium, days' supply ^a	7.28 (39.07)	13.70 (56.87)	.0003	.008	
Anticonvulsant, days' supply ^a	47.20 (105.48)	39.55 (100.86)	.062	.093	
Antidepressant monotherapy ^b	0.21 (0.40)	0.18 (0.38)	.074	.080	
Baseline comorbidity score ^a	0.45 (0.95)	0.41 (1.07)	.399	.047	
No. of claims with alcohol use diagnosis ^a	0.35 (2.07)	0.30 (2.22)	.570	.001	
No. of claims with substance use diagnosis ^a	0.40 (2.42)	0.35 (3.46)	.645	.001	
No. of claims with schizophrenia diagnosis ^a	0.16(1.73)	0.19 (1.95)	.677	.038	
No. of MH physicians ^a	1.40 (1.42)	0.59 (1.03)	< .001	.008	
Index bipolar disorder diagnosis on inpatient claim, N (%)	161 (18.79)	165 (7.29)	< .001	< .001	
Index bipolar disorder diagnosis, unspecified episode, N (%)	342 (39.91)	1,085 (47.97)	< .001	.002	

^aIn the 1-year period prior to index bipolar disorder diagnosis; data shown as mean (SD).

^bPatients treated with antidepressant monotherapy were coded 1, and those who were not treated with antidepressant monotherapy were coded 0; data shown as mean (SD).

Abbreviation: MH = mental health.

these patients, 857 (27.5%) were classified as having an OM in the follow-up period. Descriptive statistics and statistical analyses of means and proportions on select variables for the 2 cohorts are shown in Table 1. Presence of a unipolar depression diagnosis in the baseline period was a particularly strong predictor (OR = 3.22) of a depression diagnosis following the initial bipolar disorder diagnosis.

We analyzed the specialties of the health care provider giving the first depression misdiagnosis (of the 2 required for our definition of incongruent diagnosis) to see if they differed from the specialties of the health care provider who gave the index diagnosis of bipolar disorder. Within the OM cohort, 602 patients (70.2%) received their index bipolar disorder diagnosis from a mental health provider. Surprisingly, an even greater number of patients (699 [81.6%]) received the first of their unipolar depression misdiagnoses from mental health providers. In contrast, 46 patients (5.4%) received their first unipolar diagnosis from a GP, and 112 (13.1%), from another provider (hospital, 45 [5.3%]; internal medicine, 17 [2.0%]; emergency medicine, 6 [0.7%]; unknown, 44 [5.1%]). In 673 cases (78.5%), the physician giving the OM was not the physician who had diagnosed the patient with bipolar disorder.

The number of health care providers seen by patients in the year following the initial bipolar disorder diagnosis differed significantly between patient cohorts. The OM patients saw a mean of 2.9 (standard deviation [SD] = 1.9) mental health care providers versus 1.6 (SD = 1.4) for NM patients (p = .001). After controlling for propensity score and number of mental health practitioners in the year before the index bipolar disorder diagnosis, the number of visits with a mental health care provider was 1.62 times greater for OM than for NM patients. Similar results were found for GPs (mean \pm SD: OM 1.5 \pm 1.5;



NM 1.3 ± 1.4 ; p = .015; relative risk [RR] = 1.10) and for all other practitioners (OM 8.5 ± 8.1 ; NM 6.3 ± 6.4 ; p = .001; RR = 1.22).

To examine the possibility that these findings were influenced by differences in bipolar symptoms or severity between the OM and NM cohorts at their first bipolar disorder diagnosis, we examined fourth- and fifth-digit diagnosis codes. The severity indicator was available only for individual diagnostic codes 296.0, 296.1, 296.4, 296.5, and 296.6. Initial bipolar disorder diagnosis characteristics were, at best, only slightly related to later incongruent depression diagnoses (Table 2).

Diagnoses made in inpatient settings could be expected to have greater accuracy than diagnoses made in outpatient settings.²⁰ As the symptoms are severe enough to warrant hospitalization, clinicians have a greater opportunity to assess, observe, and interact with patients. For this reason, we examined the rate of later OM for patients initially diagnosed with bipolar disorder on an inpatient unit. Of the 326 individuals who received an index bipolar disorder diagnosis in an inpatient setting, 161 (49.4%) later received an incongruent unipolar depression diagnosis. For individuals diagnosed with mania on an inpatient unit, the rate remained high (24 of 58 individuals, 41.4%).

Increased Service Utilization and Costs

The OM patients had significantly more inpatient mental health visits, ER mental health visits, and ambulatory mental health visits in the follow-up period compared to NM patients (Table 3) after controlling for baseline covariates. The relative risks from the models indicated that the mean number of mental health hospital visits and ER visits were 1.82 and 2.47 times greater, respectively, for the OM patients. In addition, the mean number of mental health ambulatory visits was 1.80 times higher for OM patients than for NM patients.

After adjusting for baseline characteristics, patients in the OM cohort with any health care resource use had mean total costs of \$12,594, approximately one third more than the mean total costs of \$9405 for NM patients (Table 4). Furthermore, on average, OM patients' prescription costs were 9.9% more expensive, mental health prescription costs were 11.7% more expensive, mental health ambulatory visits were 78.7% more expensive, and mental health ER visits were 48.8% more expensive than they were for NM patients who used the same resources. These differences were statistically significant.

To integrate the 2-part model, we first derived predicted cost estimates by running 2 prediction models the first assuming the entire sample had a depression

Table 2. Initial Bipolar Disorder Diagnosis Type and Severity by Later Misdiagnosis Status

Initial Bipolar Disorder Diagnosis	Ostensible Depression Misdiagnosis (OM), N (%)	No Depression Misdiagnosis (NM), N (%)	p Value
Diagnosis type ^a			
Manic (296.0, 296.1, or 296.4)	174 (20.3)	405 (17.9)	.110
Depressed (296.5)	183 (21.4)	346 (15.3)	.0004
Mixed (296.6)	130 (15.2)	361 (16.0)	.589
Unspecified (296.7 or 296.8)	370 (43.2)	1150 (50.8)	< .0001
5th-digit indicator (296.0–296.6) ^b			
Unspecified (0)	166 (37.5)	428 (40.8)	.007
Mild (1)	20 (4.5)	60 (5.7)	.877
Moderate (2)	92 (20.8)	205 (19.5)	.206
Severe without psychotic features (3)	90 (20.3)	190 (18.1)	.065
Severe with psychotic features (4)	55 (12.4)	105 (10.0)	.045
Partial remission (5)	13 (2.9)	30 (2.9)	.757
Full remission (6)	7 (1.6)	31 (3.0)	.155

^aCohort sizes were 857 for OM and 2262 for NM.

^bSeverity information was available for 443 individuals in the OM cohort and 1049 individuals in the NM cohort.

Table 3. Mean Number of Visits by Misdiagnosis Status in the Year Following the Initial Bipolar Disorder Diagnosis

	Ostensible Depression Misdiagnosis (OM)	No Depression Misdiagnosis (NM)		
Visit Type	Adjusted Mean	Adjusted Mean	RR ^a	p Value
MH ambulatory	16.05	8.91	1.80	.001
Non-MH ambulatory	10.30	9.94	1.04	.45
MH hospital	0.39	0.21	1.82	.001
Non-MH hospital	0.15	0.14	1.12	.60
MH emergency room	0.48	0.19	2.47	.001
Non-MH emergency room	0.76	0.75	1.01	.93
^a Relative risk of increased vi background differences.	sits for the OM cohort re	lative to the NM cohort a	fter correc	ting for

Abbreviations: MH = mental health, RR = relative risk.

misdiagnosis and the second assuming the entire sample did not. We then calculated predicted probabilities of health care utilization. Predicted costs were combined with predicted probabilities of having any resource utilization (to account for individuals with 0 visits and 0 costs).

Figure 2 shows the cost differences for the various components based on this integration of the 2-part model. The largest differences between the 2 cohorts were for inpatient mental health care and mental health ambulatory care. If all patients in the study received a misdiagnosis, mean total treatment costs per person per year would be \$12,594 (median: \$11,339). If all patients received no depression misdiagnoses, mean total treatment costs would be \$9405 (median: \$8468). Thus, the increased treatment costs associated with a depression misdiagnosis were \$3189 per person per year.

An examination of the days' supply of medications in the year following the initial bipolar diagnosis revealed some differences in pharmacologic treatments for individuals receiving the incongruent unipolar depression diagnosis. Not surprisingly, the OM cohort filled prescriptions for 1.33 times as many antidepressants as the NM group (mean \pm SD: OM 326.7 ± 207.1 ; NM 261.3 ± 191.9 ; p < .001; RR = 1.33). In addition, the OM cohort filled prescriptions for 1.28 times as many atypical antipsychotics (OM 171.5 ± 148.7 ; NM 159.7 \pm 132.5; p = .003; RR = 1.28) and 1.19 times as many benzodiazepines (OM 182.3 ± 164.8 ; NM 158.0 ± 152.2 ; p = .037; RR = 1.19). However, the NM group filled significantly more prescriptions for the mood stabilizer valproate (OM 113.2 ± 79.3; NM 127.8 ± 107.2; p = .016; RR = 0.79) but filled similar amounts for lithium (OM 155.2 ± 119.1; NM 182.7 ± 131.9; p = .56; RR = 1.07).

Chart Review Results

When both the unipolar depression and bipolar disorder diagnoses were given by the same provider in the claims, both diagnoses were confirmed in only 20.8% (5/24) of the charts. The remaining chart review results refer only to the patients (N = 76) who had both a bipolar disorder chart from one provider and a depression chart from a different provider. For these pa-

tients, the unipolar depression diagnoses were confirmed in 85.5% (65/76) of the depression charts, and the bipolar disorder diagnoses were confirmed in 77.6% (59/76) of the bipolar disorder charts. When the initial bipolar disorder diagnosis and subsequent depression diagnosis were given by different providers, both diagnoses were confirmed for 65.8% (50/76) of the patients. The charts confirmed the misdiagnoses for most patients when the misdiagnoses were given by different providers but not when they were given by the same provider.

For the 65.8% (50/76) of patients in the chart review study who had confirmed bipolar disorder diagnoses and unipolar depression misdiagnoses from different providers, we examined the medications prescribed at visits with a bipolar disorder or depression diagnosis. For visits in which a bipolar disorder diagnosis was evident in the chart, patients were marginally more likely to be treated with mood stabilizers (lithium, anticonvulsants, or antipsychotics), compared with visits in which a depression diagnosis was evident in the chart (54% [27/50] vs. 36% [18/50]; p = .083), and were less likely to be treated with

Table 4. Cost Per Patient by Cohort for Individuals Who Used the Resource Type During the 1-Year Follow-Up Period (total N = 3119)

	Ostensible Depression	No Depression			Probability of Resource Use by Cohort	
Resource Type	Misdiagnosis, Adjusted Mean (costs > 0), \$	Misdiagnosis, Adjusted Mean (costs > 0), \$	R R ^a	p Value	Ostensible Depression Misdiagnosis	No Depression Misdiagnosis
Total cost for all resource types $(N = 3114)$	12,594	9,405	1.34	< .001		
MH ambulatory $(N = 2828)$	1,875	1,049	1.79	< .001	0.97	0.88
Non-MH ambulatory ($N = 2901$)	2,455	2,593	0.94	.448	0.95	0.92
MH hospital ($N = 590$)	7,447	6,177	1.21	.094	0.31	0.15
Non-MH hospital ($N = 309$)	20,255	16,944	1.19	.567	0.13	0.09
MH emergency room $(N = 319)$	897	603	1.49	.005	0.13	0.09
Non-MH emergency room $(N = 708)$	1,438	1,050	1.37	.103	0.24	0.22
MH prescription ($N = 2829$)	1,981	1,773	1.12	.014	0.95	0.89
Total prescription ($N = 3010$)	3,066	2,791	1.10	.029	0.97	0.96
^a Generalized linear models with log-link spec Abbreviations: MH = mental health, RR = rel	cification. lative risk.					



^aTotal costs were \$12,594 for the OM cohort and \$9405 for the NM cohort. Abbreviations: ER = emergency room, NM = no depression misdiagnosis, OM = ostensible depression misdiagnosis.

antidepressant monotherapy (2% [1/50] vs. 14% [7/50]; p = .034). The medication differences are in the expected direction for depression misdiagnoses.

DISCUSSION

Most of the past research on diagnostic issues and bipolar disorder has focused on the difficulty in initially recognizing the disorder. Ours is the first study we are aware of that documents the extent to which individuals "lose" a diagnosis of bipolar disorder.

More than one quarter of the patients monitored were given an OM in the year following their initial bipolar disorder diagnosis. This rate is alarmingly high, particularly considering the increased costs associated with the apparent misdiagnosis. The OM individuals had more mental health, ER, and hospital visits and more outpatient service and medication use, resulting in an increase in total treatment costs of \$3189 per person per year. The large increases in psychiatric ER and inpatient visits are indicative of psychiatric relapses and suggest that treatment associated with depression misdiagnosis was not as effective as treatment that occurred in the absence of a misdiagnosis. This finding is consistent with the idea that the majority of OM patients have true bipolar disorder and are misdiagnosed with unipolar depression, causing suboptimal treatment and poor outcomes.

Possible Mechanisms for Depression Misdiagnosis

Lack of provider education concerning bipolar disorder does not appear to be a major factor in the observed prevalence of depression misdiagnosis. More than 80% of the providers making the initial depression misdiagnosis were mental health specialists, and almost 60% of these mental health specialists were psychiatrists. In contrast, slightly fewer providers (70%) initially diagnosing bipolar disorder were mental health specialists.

 more thorough assessments are conducted, and aroundthe-clock observation of patients occurs-are more stable over time and presumably more accurate than those made during outpatient visits.²⁰ Yet, of patients who were initially diagnosed with bipolar disorder in an inpatient setting, almost one half received subsequent misdiagnoses of unipolar depression, compared with approximately one quarter of all patients in the OM cohort. This discrepancy could be explained by the disruption in continuity of care that occurs following discharge from an inpatient facility. This result is consistent with the findings of Keck and colleagues,¹² who found that one half of patients become noncompliant with medication during the 12-month period after hospitalization for bipolar mania, primarily because they believe they are not ill. Better patient follow-up after discharge from inpatient facilities could potentially reduce treatment costs and improve treatment outcomes.

The most common reason for the high rates of depression misdiagnosis in the current study appears to be gaps in continuity of care, compounded by the erratic and diagnostically challenging nature of bipolar disorder. In most cases (78.5%) in the current study, the first misdiagnosis was given by a different physician than the one who had previously identified the bipolar disorder. Furthermore, the chart review confirmed that the depression misdiagnoses identified in the claims data were in the charts in most cases (65.8%) when different providers gave the bipolar disorder and depression diagnoses. If no information regarding the past symptoms of mania or hypomania is being communicated, provider switching could lead to the misdiagnosis of bipolar disorder as depression. To be able to properly diagnose bipolar disorder, a physician needs longitudinal knowledge of a patient's symptoms; that way, the physician can identify current depressive symptoms as part of a "larger" bipolar disorder rather than as a separate depressive disorder. With only information about current symptoms, a diagnosis of depression-a more prevalent disorder²¹—would be more reasonable.

Health care providers face a number of barriers to accurate information about a patient's medical history, including inaccurate patient communication and poor patient acceptance and understanding of their bipolar disorder diagnosis. When asked, individuals with bipolar disorder generally do not recall past manic episodes or do not recall them as being problematic.⁸ In addition, a patient may not accept a diagnosis of bipolar disorder because of its negative social stigma.²² In the current study, 61% (519/857) of those who received the apparent misdiagnosis had a depression diagnosis prior to their bipolar disorder diagnosis compared to only 18% (411/2262) of those with no misdiagnosis (Table 1). Some patients may have switched providers because they did not agree with the bipolar disorder diagnosis and preferred a diagnosis of depression. Finally, patients may not have been aware of the past bipolar disorder diagnosis. Makaryus and Friedman²³ found that only 41.9% of patients are able to correctly state their diagnosis following medical hospitalization. Compounding this difficulty, physicians cannot always get patient records. Mitchell and colleagues²⁴ reported that a requesting physician receives medical records only 64.6% of the time.

Increased Costs

The mean cost increase of \$3189 per incongruent depression diagnosis is striking. Examination of the cost components showed increased mental health cost components across the board: inpatient, emergency, medication, and ambulatory care. Of particular concern was the dramatic rise in psychiatric inpatient and ER costs. These acute care costs generally represent instances of expensive psychiatric relapses²⁵ that appear to reflect worse outcomes associated with increased treatment for depression rather than bipolar disorder. Annual treatment costs for depression are generally lower than the costs for bipolar disorder.^{6,26} If the depression diagnosis had been the correct diagnosis from the beginning, we would not expect to see the large cost increase.²⁷

Although this is a fairly rudimentary analysis given the complex medication treatment patterns for bipolar disorder, the comparisons of days' supply of different medications in the claims data support the notion that OM bipolar patients were receiving inappropriate treatment leading to increased manic relapses. First, as expected, there was a greater use of antidepressants among the OM patients. Antidepressants are not recommended for monotherapy use in the treatment of bipolar depression because of potential for inducing mania^{14,15} and increasing cycling.^{16,28} Second, for the treatment of mania, the American Psychiatric Association's practice guidelines²⁸ recommend first-line use of atypical antipsychotics, lithium, valproate, or the combination of these medications, as well as potential, short-term, adjunctive use of benzodiazepines. The greater use of atypical antipsychotics and benzodiazepines among the OM group appears to represent more frequent treatment of manic symptoms. Finally, for maintenance treatment, the guidelines²⁸ suggest using valproate or lithium monotherapy as first-line treatment. The reduced use of divalproex for the patients receiving the apparent depression misdiagnoses suggests that they were less likely to receive the needed maintenance treatment. The observed pattern of pharmacologic treatments between the OM and NM groups is consistent with the OM group's being more likely to be treated for depression than for bipolar disorder, resulting in greater rates of manic relapses.

The difference in cost between the OM and NM patient cohorts does not appear to be a result of more complex or more complicated bipolar disorder symptoms in the OM cohort. We examined the initial bipolar disorder diagnostic type (4-digit code) and severity indicator (fifth digit for codes 296.0–296.6 only) and found very few meaningful differences (Table 2). Although this examination does not provide conclusive evidence, it does not support the notion that the initial bipolar disorder symptoms varied significantly.

Limitations

In this study, information on patient diagnosis was derived from administrative claims data. Claims algorithms for detecting other diseases, such as Alzheimer's disease²⁹ and myocardial infarction,³⁰ have been demonstrated to be predictive of the condition. In our chart review, our algorithms were shown to be reasonably predictive of chart diagnoses, with a positive predictive value of 85.5% for unipolar depression and 77.6% for bipolar disorder. These values may represent a lower bound given that we examined only 1 or 2 charts per patient and that the claims data may contain diagnoses from providers other than those whose charts we reviewed. However, even if the claims diagnoses were confirmed in the charts, we cannot be certain that the chart diagnoses were accurate.

Although we used state-of-the-art propensity score techniques, adjusting for a wide variety of background and disease-state variables (Table 1), we cannot fully rule out the possibility that the observed cost differences between OM and NM patients were the result of a factor that was not accounted for in propensity scores. Future research is needed to prospectively follow patients first diagnosed with bipolar disorder (potentially using administrative claims data) to verify that an intervention could prevent the later depression misdiagnoses and corresponding relapses and health care costs.

SUMMARY AND CONCLUSIONS

More than one quarter of patients diagnosed with bipolar disorder were subsequently given apparent misdiagnoses of unipolar depression in administrative claims data. These misdiagnoses seemed to result in more frequent suboptimal treatment and greater rates of relapses for these patients, given the evidence of increased use of acute psychiatric service and corresponding increased health care costs, coupled with the pattern of psychotropic medication use observed in the claims data. Misdiagnoses of unipolar depression appear to result primarily from poor continuity of care. Interventions that facilitate health care provider access to patient histories could reduce the prevalence of this type of misdiagnosis. This reduction in misdiagnosis in turn could both improve patient outcomes and potentially reduce treatment costs by \$3000 per year for each prevented misdiagnosis.

Drug names: divalproex (Depakote), lithium (Eskalith, Lithobid, and others).

Author contributions: As an employee of Eli Lilly and Company, Dr. Stensland was involved with designing the study, analyzing and interpreting the data, and writing and reviewing the manuscript. The sponsor reviewed the manuscript prior to submission. Dr. Schultz had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Frytak was involved with designing the study, interpreting the data, and reviewing the manuscript.

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