# Economic Consequences of Not Recognizing Bipolar Disorder Patients: A Cross-Sectional Descriptive Analysis

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***Background:*** This retrospective study compared treatment patterns and costs for patients with recognized and unrecognized bipolar disorder with those of depressed patients without a bipolar disorder claim.

***Method:*** Claims data for 7 large national employers covering 585,584 persons aged less than 65 years were used to identify patients diagnosed with depression and initially treated with antidepressants. Data on employees, as well as spouses and dependents, for the period 1998 to mid-2001 were used. Patients were identified as bipolar based on the criteria of a bipolar diagnosis claim (ICD-9 codes: 296.0, 296.1, 296.4–296.8) and/or a mood stabilizer prescription claim. Of the patients identified as bipolar, unrecognized bipolar disorder (unrecognized-BP) patients met the criteria after antidepressant initiation, while recognized bipolar disorder (recognized-BP) patients met the criteria at or before initiation. The remaining patients in the sample were non-bipolar depressed (non-BP) patients. Outcome measures included treatment patterns and monthly medical costs in the 12 months subsequent to initiation of antidepressant treatment.

***Results:*** Of the 9009 patients treated for depression with antidepressants, there were 8383 non-BP patients (93.1%), 293 recognized-BP patients (3.3%), and 333 unrecognized-BP patients (3.7%). Use of combination therapies varied among the non-BP (11%), unrecognized-BP (32%), and recognized-BP patients (44%) (all pairwise $p < .01$). Use of mood stabilizers was less frequent among unrecognized-BP patients (14%) than recognized-BP patients (34%) ($p < .0001$). Unrecognized-BP patients incurred significantly greater ($p < .05$) mean monthly medical costs ($1179) in the 12 months following initiation of antidepressant treatment compared with recognized-BP patients ($801) and non-BP patients ($585). Monthly indirect costs were significantly greater ($p < .05$) for unrecognized-BP ($570) and recognized-BP ($514) employees compared with non-BP employees ($335) in the 12 months following antidepressant initiation.

***Conclusions:*** Patterns of medication treatment for bipolar disorder were suboptimal. Accurate and timely recognition of bipolar disease was associated with lower medical costs and lower indirect costs due to work loss.

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With an estimated prevalence ranging from 1% to 8%,[1,2] the misdiagnosis of bipolar disorder, particularly as unipolar depression, poses a threat to the proper treatment of bipolar disorder.[3] In a study by Ghaemi et al.,[4] 40% of patients with bipolar disorder had previously received an incorrect diagnosis of major depression. Angst and colleagues[5] reported that 25% to 50% of all major depression cases were bipolar. Similar data were found for respondents to a survey of the National Depressive and Manic-Depressive Association, among whom major depression was the most common misdiagnosis, with 57% of the members receiving a major depression diagnosis prior to a bipolar disorder diagnosis.[6] This survey reported that 70% of persons with bipolar disorder are initially misdiagnosed and that prior to receiving an accurate diagnosis, half of patients diagnosed with bipolar disorder had consulted 3 or more physicians or other professionals.[6] On average, it took 8 years before the bipolar disorder diagnosis was correctly made.[7]

While efforts have been made to correctly recognize and diagnose bipolar disorder, little progress has been reported. Diagnosis of bipolar disorder is least complex in depressed patients with an unequivocal manic episode. In those without such an episode, there are some differentiators for bipolar disorder (as opposed to unipolar depression), which include more mood stability[8] and sleep time.[9] Other factors suggestive of bipolar disorder include early age at onset, frequency of depressive episodes, a greater percentage of time ill, and a relatively acute onset of symptoms.[10] However, a number of similarities can contribute to the misdiagnosis of bipolar disorder as unipolar depression.[11] First, bipolar disorder

often starts as major depression in the period from childhood to young adulthood. Because DSM-IV criteria require a presentation of manic or hypomanic episode prior to making a bipolar disorder diagnosis, many patients are initially diagnosed and subsequently treated for major depression. Second, since depression usually causes more subjective distress than does mania, patients' lack of insight into mania can lead to misdiagnosis, as they are more likely to seek help for depression than for mania.[12] Third, the greater social acceptability and awareness of depression and the increased availability and success of antidepressants may influence the diagnosis of unipolar depression, with subsequent antidepressant treatment, and result in a misdiagnosis and mistreatment of bipolar disorder.

Misdiagnosis and consequent mistreatment of bipolar disorder as unipolar depression generally lead to missed opportunities for early therapeutic intervention, with resultant clinical consequences. Misdiagnosis can lead to delays in efficacious treatment with mood stabilizers (e.g., lithium). Li et al.[13] found that direct health care costs were significantly higher among patients who delayed use of or did not use mood stabilizers during their first year of bipolar disorder therapy. When mood-stabilizing treatment is eventually initiated for patients who have had unsuccessful treatment for several depressive episodes of illness, the treatment may be less effective.[14] Furthermore, because the profile of antidepressant effects is different in bipolar disorder as opposed to unipolar depression, misdiagnosis as unipolar depression may lead to serious clinical consequences. In contrast to their effects on unipolar depression, antidepressants have not been shown to prevent depression among bipolar patients.[15] In addition, antidepressant treatment among bipolar patients can have a destabilizing effect on the course of illness and lead to an induction or cycling into the manic and hypomanic phases of the disorder.[16–18]

The literature on the economic burden of bipolar disorder documents its substantial costs. For example, one widely cited report estimates that the total economic burden of bipolar disorder in the United States was $45 billion in 1991, of which only $7 billion was due to actual treatment costs.[19] While this estimate of bipolar disorder costs may be excessive, bipolar disorder undoubtedly represents a significant economic burden. Research by Greenberg et al.[20] suggests that the annual cost of bipolar disorder in 1990 in the United States was approximately $10 billion. Another study found that the lifetime costs for all persons in the United States with bipolar disorder onset in 1998 were $24 billion.[21] At the patient level, a study using 1996 claims data found that the average annual treatment cost of patients with at least 1 hospitalization for mania was approximately $17,000.[22] Another study of patients with claims for depression found that more severe depression was associated with greater episode inpatient treatment costs, with 1989 payments of $1233, $2501, and $2971 for depression not otherwise specified, major depression, and bipolar disorder, respectively.[23] A recent study over a 1-year period (1997) found that bipolar patients utilized nearly 3 to 4 times the health care resources and incurred over 4 times greater costs per patient compared with an age- and sex-matched non-bipolar group during the 1-year period ($7663 vs. $1962) and that patients with bipolar disorder (among the single bipolar diagnostic categories of mixed, manic, or depressed) incurred the highest health care costs.[24]

Bipolar disorder affects patients in many aspects of their lives, leading to an increase in their indirect cost. One study found that less than half of bipolar patients discharged from a psychiatric hospitalization were employed 6 months after discharge.[25] Moreover, bipolar disorder is associated with high rates of family discord (e.g., divorce, adjustment problems among children, legal problems).[6] Therefore, it is not surprising that among physical and psychiatric disorders, bipolar disorder is the sixth highest cause of disability.[26]

Economic consequences are also found in patients with unrecognized bipolar disorder, who are frequently misdiagnosed as having unipolar depression. One study that used the paid claims data (1993–1999) from the California Medicaid program found that unrecognized bipolar disorder patients have higher rates of hospital use and attempted suicide compared with recognized bipolar disorder patients.[27] Therefore, it is warranted to investigate differences in costs between depressed patients with recognized and unrecognized bipolar disorder, as well as between bipolar disorder and non-bipolar depressed patients.

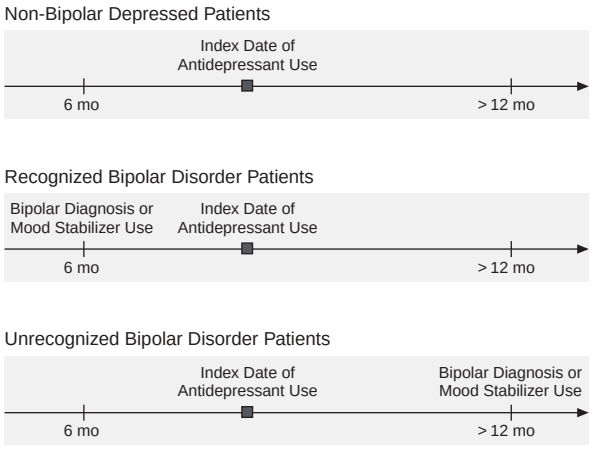
The objective of this retrospective claims data study in a sample of patients with depression diagnosis who were initially treated with antidepressants was to analyze the extent to which the treatment patterns and costs (direct and indirect costs) of unrecognized bipolar patients are different from those of non-bipolar depressed patients and recognized bipolar patients. As a cross-sectional, descriptive analysis, this research was meant to generate hypotheses for future research.

## METHOD

### Data Source

The analysis used de-identified (i.e., encrypted) employer administrative data provided by Ingenix (New Haven, Conn.) for 7 large national employers covering 585,584 persons aged less than 65 years. The companies represented a broad range of industries (including manufacturing, telecommunications, financial services, and food and beverage companies) and various types of occupations (including factory, sales, office, scientific, clerical, management, etc.). Managed care claims for

**Figure 1. Classification and Treatment Course of Bipolar and Non-Bipolar Patients Receiving an Antidepressant for Depression**




employees, as well as spouses and dependents, for the period 1998 to mid-2001 were included and covered all regions of the United States. The data included medical and drug prescription claims for all beneficiaries, as well as work loss claims for employees eligible for short- and long-term disability. Patients with a recorded bipolar disorder diagnosis (ICD-9 codes 296.0, 296.1, 296.4–296.8) were identified to obtain a prevalence rate (0.5%) in this database.

## Inclusion and Exclusion Criteria

Patient selection criteria were defined a priori in the research protocol. The majority of the criteria were defined by diagnostic codes and the timing of the first antidepressant treatment. Post hoc criteria were incorporated to account for the possibility of treatment-refractory patients. However, no modifications were made in the criteria after the results of the measures were reviewed.

For the research sample, 3142 patients with a bipolar disorder diagnosis who were aged 18 to 64 years were selected. Of this group, 1709 patients with a diagnosis of depression (i.e., at least 1 claim for ICD-9 296.2, 296.3, 300.4, 309.0, 309.1, or 311) were initially treated with an antidepressant. The depression diagnosis could have occurred at any point for which data were available (1998 to mid-2001), regardless of the timing of the index date. An index date was defined as the date of the first antidepressant prescription claim following a washout period of at least 6 months during which there was no antidepressant claim. Patients had to have at least 1 index date (this date is patient specific and the earliest for patients who could have had multiple index dates), which restricted the sample to 890 patients. Furthermore, all patients also had to have at least 12 months of data following their first index date, which restricted the sample further to 626 patients (of the 3142 bipolar patients) who met all requirements for the research sample.

Figure 1 illustrates how we further identified a subset of bipolar patients and classified comparison groups from this research sample, based on a bipolar disorder diagnosis claim (i.e., at least 1 claim with an ICD-9 code of 296.0, 296.1, or 296.4–296.8) and/or a mood stabilizer (lithium or valproate) claim. Of these bipolar disorder patients, unrecognized bipolar disorder (unrecognized-BP) patients received an initial bipolar disorder diagnosis and/or mood stabilizer prescription after the first index date, while recognized bipolar disorder (recognized-BP) patients had these records on or before the first index date. The remaining patients in the research sample were non-bipolar depressed (non-BP) patients.

Post hoc selection criteria were added to exclude patients with treatment-refractory depression from this subset of bipolar patients. We focused on those patients with only mood stabilizer prescriptions after their index date (i.e., no bipolar diagnosis claims). For these patients, we retained only those who discontinued their antidepressant treatment for at least 15 days before through 15 days after the initiation of their mood stabilizer treatment. In addition, a post hoc sensitivity analysis for total costs in the 12 months following antidepressant initiation was performed from which these patients with only mood stabilizer claims were dropped. As a result, 43 patients identified only because of use of a mood stabilizer were excluded.

As an additional post hoc exploratory analysis, unrecognized-BP and recognized-BP patients were further examined to identify plausibly induced bipolar patients based on the specific ICD-9 codes of the first bipolar mania claim after the first index date. Specifically, plausibly induced bipolar patients were defined as those who manifested mania as indicated by ICD-9 codes of 296.0 and 296.4 within 6 months after starting an antidepressant.

## Analysis

***Outcomes.*** The analysis was centered at the patient-specific index date, which for all patients was the first date of an antidepressant claim following a washout period of at least 6 months. Outcome measures were mean monthly treatment costs (direct and indirect) in the 6 months before and the 12 months after the index date and treatment patterns (use of combination treatment and use of mood stabilizers) in the 12 months following the antidepressant initiation. Direct costs were calculated based on payments to health care providers for inpatient, outpatient, physician, and prescription drug services, as well as for other ancillary services (e.g., physical therapy, home health services). Direct costs (measured as payments to providers by the employer/insurer or beneficiary) were calculated for all of the company's bene-

**Table 1. Demographic Data for Patients Treated for Depression With Antidepressants**

| Variable | Research Sample (N = 9009) | Non-BP Patients[a] (N = 8383) | Recognized-BP Patients[b] (N = 293) | Unrecognized-BP Patients[c] (N = 333) |
|---|---|---|---|---|
| Age, N (%) | | | | |
| 18–35 y | 1802 (20.0) | 1662 (19.8) | 70 (23.9) | 70 (21.0) |
| 36–45 y | 2213 (24.6) | 2057 (24.5) | 71 (24.2) | 85 (25.5) |
| 46–55 y | 3396 (37.7) | 3164 (37.7) | 101 (34.5) | 131 (39.3) |
| 56–64 y | 1598 (17.7) | 1500 (17.9) | 51 (17.4) | 47 (14.1) |
| Age, mean, y[d,e] | 45.0 | 45.1 | 43.5 | 43.8 |
| Gender, N (%)[e] | | | | |
| Male[d,e] | 2395 (26.6) | 2243 (26.8) | 79 (27.0) | 73 (21.9) |
| Female[d,e] | 6614 (73.4) | 6140 (73.2) | 214 (73.0) | 260 (78.1) |
| Relation, N (%) | | | | |
| Employee[e] | 5268 (58.5) | 4931 (58.8) | 156 (53.2) | 181 (54.4) |
| Active[d,e] | 4368 (82.9) | 4152 (84.2) | 113 (72.4) | 143 (79.0) |
| Retired[d,e] | 805 (15.3) | 732 (14.8) | 37 (23.7) | 36 (19.9) |
| Other[d–f] | 55 (1.0) | 47 (1.0) | 6 (3.8) | 2 (1.1) |
| Spouse | 2951 (32.8) | 2750 (32.8) | 89 (30.4) | 112 (33.6) |
| Adult dependents[d,e] | 790 (8.8) | 702 (8.4) | 48 (16.4) | 40 (12.0) |

[a]Non-bipolar patients who did not have a claim for a bipolar condition or a mood stabilizer prescription at any time.
[b]Recognized bipolar patients who had either a diagnosis for a bipolar condition or a mood stabilizer prescription (or both) prior to their first index date.
[c]Unrecognized bipolar patients who had no diagnosis for a bipolar condition or a mood stabilizer prescription prior to their first index date but did have a claim for either or both after their first index date.
[d]Non-BP significantly different from recognized-BP ($p < .05$).
[e]Non-BP significantly different from unrecognized-BP ($p < .05$).
[f]Includes leave of absence, terminated, surviving dependent, and Consolidated Omnibus Budget Reconciliation Act (COBRA) employees.

beneficiaries. Indirect costs were calculated only for employees, based on payments by the employer for disability claims and imputed wages for medically related work absence days (e.g., days in the hospital, days of work absence required before initiation of disability coverage).

***Hypotheses.*** We hypothesized that unrecognized bipolar disorder led to increased costs in the 12 months subsequent to the index date because, even though patients in this group may have been diagnosed correctly, they may not have been managed effectively and thus may have incurred higher costs than recognized-BP and non-BP patients. The analysis also examined the costs for all 3 samples in the 6 months prior to the index date, and we hypothesized that recognized-BP patients incurred more costs than non-BP patients due to treatment of bipolar disorder.

***Statistical analyses.*** The economic component of this analysis involved a descriptive analysis of the direct (i.e., medical treatment) and indirect (i.e., work loss) costs for the 3 samples. Treatment patterns (use of combination treatment and use of mood stabilizers) were also compared across the 3 samples. In addition, we measured the prevalence rate of treatment based on a recorded bipolar diagnosis in the claims data, the rates of unrecognized-BP and recognized-BP among patients treated for depression with antidepressants, and the rates of plausible mania induction. These descriptive statistics were generated using version 8 of the statistical software program SAS.[28] The statistical significance of the differences in outcomes and rates of utilization between the samples were measured using t tests, with significance measured at $p < .05$.

## RESULTS

### Prevalence Rates, Demographics, and Illness Characteristics

Of the research sample of 9009 patients treated for depression with antidepressants, 626 (7%) were bipolar disorder patients. The sample contained 333 unrecognized-BP patients (3.7%) and 293 recognized-BP patients (3.3%). Plausibly induced bipolar disorder patients represented 7.5% of all bipolar patients in the research sample (47/626).

The bipolar disorder patients were similar to the non-BP patients in terms of demographics. The majority (over 70%) of both non-BP and bipolar patients were women. However, while slightly more than half of both the non-BP and bipolar patients were employees, a greater percentage of non-BP patients were actively employed, and a greater percentage of both the recognized-BP and unrecognized-BP employees were early retirees. The mean age of patients was somewhat older in the non-BP sample than in both the recognized-BP and unrecognized-BP samples. There was a significantly larger percentage of adult dependents in the bipolar samples than in the non-BP sample (Table 1).

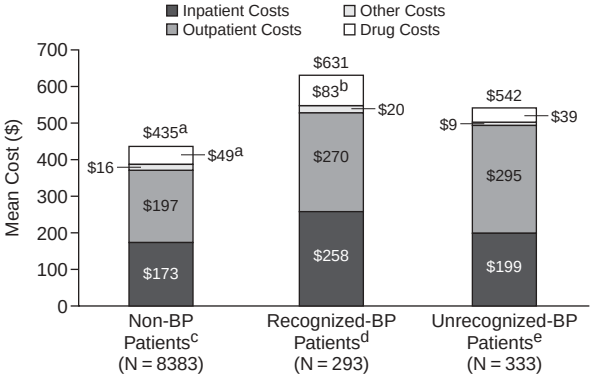
Recognized-BP patients had significantly higher rates of mental illness comorbidity than both non-BP and unrecognized-BP patients in the 6 months prior to initia-

**Table 2. Incidence of Comorbidities Among the Non-BP, Recognized-BP, and Unrecognized-BP Groups in the 6 Months Before First Index Date, %**

| Variable | Non-BP Patients[a] (N = 8383) | Recognized-BP Patients[b] (N = 293) | Unrecognized-BP Patients[c] (N = 333) |
|---|---|---|---|
| Schizophrenia | 0.36[d] | 2.39 | 1.50 |
| Other psychosis[e] | 0.69[d] | 20.48[f] | 1.80 |
| Other personality disorder[g] | 9.79[d] | 16.38[f] | 9.91 |
| Any mental illness[h] | 10.63[d] | 33.11[f] | 12.61 |
| Alcohol and drug abuse | 1.53 | 3.07 | 2.10 |
| Emergency room visit | 2.35 | 2.05 | 3.90 |
| Hospitalized for any psychiatric disorder | 2.59[d,i] | 15.36[f] | 6.01 |

[a]Non-bipolar patients who did not have a claim for a bipolar condition or a mood stabilizer prescription at any time.
[b]Recognized bipolar patients who had either a diagnosis for a bipolar condition or a mood stabilizer prescription (or both) prior to their first index date.
[c]Unrecognized bipolar patients who had no diagnosis for a bipolar condition or a mood stabilizer prescription prior to their first index date but did have a claim for either or both after their first index date.
[d]Non-BP significantly different from recognized-BP ($p < .05$).
[e]Includes other affective psychoses, paranoid states, other nonorganic psychoses, and psychoses originating in childhood (ICD-9: 296.9x, 297.x, 298.x, 299.x).
[f]Recognized-BP significantly different from unrecognized-BP ($p < .05$).
[g]Includes anxiety states and personality disorders (ICD-9: 300.x and 301.x).
[h]Includes patients with schizophrenia, other psychosis, or personality disorder.
[i]Non-BP significantly different from unrecognized-BP ($p < .05$).

**Figure 2. Monthly Direct Costs Incurred in the 6 Months Before Index Date (all patients)**




[a]Non-BP significantly different from recognized-BP ($p < .05$).
[b]Recognized-BP significantly different from unrecognized-BP ($p < .05$).
[c]Non-bipolar patients who did not have a claim for a bipolar condition or a mood stabilizer prescription at any time.
[d]Recognized bipolar patients who had either a diagnosis for a bipolar condition or a mood stabilizer prescription (or both) prior to their first index date.
[e]Unrecognized bipolar patients who had no diagnosis for a bipolar condition or a mood stabilizer prescription prior to their first index date but did have a claim for either or both after their first index date.

tion of antidepressant treatment (all statistically significant, except for the non-BP vs. unrecognized-BP comparison) (Table 2). Both recognized-BP and unrecognized-BP patients were significantly more likely to be hospitalized for any psychiatric disorder than non-BP patients, and recognized-BP patients had significantly higher rates than unrecognized-BP patients.

### Treatment Patterns

The rate of combination therapy, defined as the use of mood stabilizers, antipsychotics, anticonvulsants, or other antidepressants concomitantly during antidepressant therapy, varied among the non-BP, unrecognized-BP, and recognized-BP patients (11%, 32%, and 44%, respectively) (all pairwise $p < .01$). The use of mood stabilizers was significantly less frequent among unrecognized-BP patients than recognized-BP patients (14% and 34%, respectively; $p < .0001$). Among unrecognized-BP patients, the most frequent combination therapy was the addition of a second antidepressant (37%).

### Costs

Direct (i.e., medical) costs for all non-BP and bipolar patients incurred in the 6 months before initiation of antidepressant therapy are presented, followed by costs in the 12 months following the initiation of antidepressant therapy. The direct and indirect (i.e., work loss) costs for active employees in those time periods are also presented.

In the 6 months before the initiation of antidepressant therapy, recognized-BP patients had significantly greater total direct costs on a monthly basis than non-BP patients (mean [SD] = $631 [$917] vs. $435 [$1335] for recognized-BP and non-BP patients, respectively). However, the recognized-BP versus unrecognized-BP cost differences were statistically significant only for prescription drugs (Figure 2).

In the 6 months before the initiation of antidepressant therapy, recognized-BP active employees had significantly greater monthly indirect costs ($766) than non-BP employees ($304). However, non-BP and unrecognized-BP active employee monthly indirect costs were similar ($304 vs. $371) (Table 3).

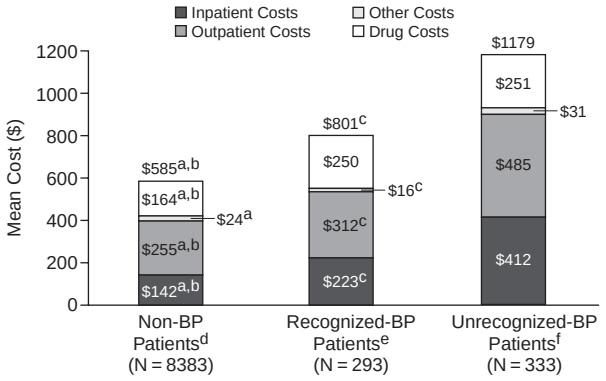
In the 12 months following the initiation of antidepressant therapy, unrecognized-BP patients had significantly greater total direct costs ($1179 [$1530]) compared with recognized-BP ($801 [$729]) and non-BP patients ($585 [$1187]), while recognized-BP patients had significantly greater costs than non-BP patients. There were very similar patterns of significant differences across major components (e.g., inpatient, outpatient, and pharmacy) of direct medical costs. For example, the monthly inpatient costs for unrecognized-BP patients ($412 [$974]) were almost 3 times the corresponding costs for non-BP patients ($142 [$1029]), and monthly outpatient costs were almost twice as much for unrecognized-BP ($485

**Table 3. Monthly Costs Incurred in the 6 Months Before Index Date (active employees only)**

| Type of Cost | Non-BP[a] (N = 4152) Cost ($), Mean (SD) | % of Total Cost | % of Patients With Claim | Recognized-BP[b] (N = 113) Cost ($), Mean (SD) | % of Total Cost | % of Patients With Claim | Unrecognized-BP[c] (N = 143) Cost ($), Mean (SD) | % of Total Cost | % of Patients With Claim |
|---|---|---|---|---|---|---|---|---|---|
| Direct | | | | | | | | | |
| Medical | | | | | | | | | |
| Hospital inpatient | 154 (1156) | 21.9 | 9.7 | 264 (813) | 18.8 | 22.1 | 131 (628) | 15.0 | 10.5 |
| Outpatient[d] | 185 (482)[e,f] | 26.3 | 90.3 | 286 (366) | 20.3 | 95.6 | 329 (1611) | 37.6 | 88.8 |
| Other[g] | 17 (230) | 2.4 | 30.3 | 12 (30) | 0.9 | 30.1 | 9 (33) | 1.0 | 27.2 |
| Drugs | 43 (104)[e] | 6.1 | 74.1 | 79 (160)[h] | 5.6 | 79.9 | 35 (59) | 4.0 | 69.1 |
| | Mean | | | Mean | | | Mean | | |
| Subtotal | 399[e] | 56.8 | | 641 | 45.6 | | 504 | 57.6 | |
| Indirect | 304[e] | 43.2 | | 766 | 54.4 | | 371 | 42.4 | |
| Total | 703[e] | 100.0 | | 1407 | 100.0 | | 875 | 100.0 | |

[a]Non-bipolar patients who did not have a claim for a bipolar condition or a mood stabilizer prescription at any time.
[b]Recognized bipolar patients who had either a diagnosis for a bipolar condition or a mood stabilizer prescription (or both) prior to their first index date.
[c]Unrecognized bipolar patients who had no diagnosis for a bipolar condition or a mood stabilizer prescription prior to their first index date but did have a claim for either or both after their first index date.
[d]Includes both hospital outpatient claims and office claims.
[e]Non-BP significantly different from recognized-BP ($p < .05$).
[f]Non-BP significantly different from unrecognized-BP ($p < .05$).
[g]Costs found in extended care facilities, nursing homes, laboratories, home care, hospice, etc.
[h]Recognized-BP significantly different from unrecognized-BP ($p < .05$).

**Figure 3. Monthly Direct Costs Incurred in the 12 Months Following Index Date (all patients)**




[a]Non-BP significantly different than recognized-BP ($p < .05$).
[b]Non-BP significantly different than unrecognized-BP ($p < .05$).
[c]Recognized-BP significantly different than unrecognized-BP ($p < .05$).
[d]Non-bipolar patients who did not have a claim for a bipolar condition or a mood stabilizer prescription at any time.
[e]Recognized bipolar patients who had either a diagnosis for a bipolar condition or a mood stabilizer prescription (or both) prior to their first index date.
[f]Unrecognized bipolar patients who had no diagnosis for a bipolar condition or a mood stabilizer prescription prior to their first index date but did have a claim for either or both after their first index date.

[$1152]) versus non-BP patients ($255 [$487]). Additionally, unrecognized-BP patients had significantly higher costs for hospital inpatient and outpatient services than recognized-BP patients ($412 [$974] and $485 [$1152] for unrecognized-BP vs. $223 [$577] and $312 [$368] for recognized-BP). Monthly pharmacy costs for recognized-BP ($250 [$249]) and unrecognized-BP ($251 [$217]) patients were similar, but both were significantly higher than those for non-BP patients ($164 [$203]) (Figure 3).

The increased costs in the 12 months after the initiation of antidepressant therapy reflected unrecognized-BP patients' statistically significantly higher rate of utilization for all medical services than non-BP and recognized-BP patients. For example, 40% of unrecognized-BP patients had an inpatient hospital stay, versus only 29% and 16% of recognized-BP and non-BP patients, respectively. Indeed, unrecognized-BP patients also used more outpatient and other services than did recognized-BP and non-BP patients.

Patterns in direct monthly costs for active employees were consistent with those for the patient samples in the 12 months following the index date. Monthly direct costs in the 12 months after the initiation of antidepressant therapy were significantly greater for recognized-BP and unrecognized-BP active employees than for non-BP active employees. Recognized-BP and unrecognized-BP active employees also had significantly greater indirect costs compared with those of non-BP active employees. Specifically, non-BP active employees incurred $335 in indirect costs, while recognized-BP and unrecognized-BP active employees incurred $514 and $570, respectively. Both recognized-BP and unrecognized-BP active employees had similar indirect costs as calculated by their disability payments and their medical work loss (Table 4).

Since the use of a mood stabilizer may indicate that a patient has treatment-refractory depression rather than bipolar disorder, we conducted a sensitivity analysis in which only patients with a bipolar disorder diagnosis were included. Accordingly, there were 324 unrecognized-BP-only and 259 recognized-BP-only patients. While the

**Table 4. Monthly Costs Incurred in the 12 Months Following Index Date (active employees only)**

| | Non-BP[a] (N = 4152) | | | Recognized-BP[b] (N = 113) | | | Unrecognized-BP[c] (N = 143) | | |
|---|---|---|---|---|---|---|---|---|---|
| Type of Cost | Cost ($), Mean (SD) | % of Total Cost | % of Patients With Claim | Cost ($), Mean (SD) | % of Total Cost | % of Patients With Claim | Cost ($), Mean (SD) | % of Total Cost | % of Patients With Claim |
| Direct | | | | | | | | | |
| Medical | | | | | | | | | |
| Hospital inpatient | 110 (870)[d] | 13.2 | 14.3 | 186 (554) | 14.9 | 25.6 | 350 (1017) | 20.1 | 36.4 |
| Outpatient[e] | 233 (233)[d,f] | 28.0 | 97.4 | 325 (355) | 26.0 | 100.0 | 568 (1657) | 32.6 | 99.3 |
| Other[g] | 17 (115)[f] | 2.0 | 48.3 | 9 (18)[h] | 0.7 | 50.4 | 20 (63) | 1.1 | 55.9 |
| Drugs | 138 (187)[d,f] | 16.6 | 98.6 | 215 (196) | 17.2 | 98.6 | 235 (218) | 13.5 | 99.1 |
| | Mean | | | Mean | | | Mean | | |
| Subtotal | 498[d,f] | 59.8 | | 735[h] | 58.8 | | 1173 | 67.3 | |
| Indirect | 335[d,f] | 40.2 | | 514 | 41.1 | | 570 | 32.7 | |
| Total | 833[d,f] | 100.0 | | 1249 | 100.0 | | 1743 | 100.0 | |

[a]Non-bipolar patients who did not have a claim for a bipolar condition or a mood stabilizer prescription at any time.
[b]Recognized bipolar patients who had either a diagnosis for a bipolar condition or a mood stabilizer prescription (or both) prior to their first index date.
[c]Unrecognized bipolar patients who had no diagnosis for a bipolar condition or a mood stabilizer prescription prior to their first index date but did have a claim for either or both after their first index date.
[d]Non-BP significantly different from unrecognized-BP ($p < .05$).
[e]Includes both hospital outpatient claims and office claims.
[f]Non-bipolar depressed significantly different from recognized-BP ($p < .05$).
[g]Costs found in extended care facilities, nursing homes, laboratories, home care, hospice, etc.
[h]Recognized-BP significantly different from unrecognized-BP ($p < .05$).

costs dropped somewhat, the overall pattern remained the same for this BP-only group. Among the BP-only patients, in the 6 months before the initiation of antidepressant therapy, unrecognized BP-only patients had lower total direct costs ($516 [$1697]) compared with recognized BP-only patients ($559 [$995]), although the difference was no longer of statistical significance. Among the BP-only patients, in the 12 months following the initiation of antidepressant therapy, unrecognized BP-only patients had significantly greater total direct costs ($953 [$1694]) compared with recognized BP-only patients ($579 [$819]).

## DISCUSSION

This analysis used a rich source of administrative claims for privately insured beneficiaries of large employers. Because the analysis relied on insurance claims data, the results are subject to the usual limitations of analyses of administrative datasets regarding the accuracy of medical diagnosis and the possible incomplete collection of claims. These limitations include the possibilities of inaccurate diagnoses, coding inaccuracies (which are particularly an issue in this case study for both diagnoses of bipolar disorder and depression), and missing data.[29] However, we recognize that correct diagnosis of bipolar disorder will never be 100% accurate (at least until some definitive biological marker is discovered), and thus the unfortunate process of first diagnosing bipolar patients with depression most likely will continue, at least to a certain extent.

There are potential selection biases associated with the possibility that bipolar disorder may be underreported in claims data due to social stigma, practice differences between primary care physicians and specialists, and other factors. The data are also restricted to patients who were identified on the basis of their antidepressant treatment for bipolar disorder. This restriction has 2 kinds of implications for patient selection. First, patients in the database who may have bipolar disorder but received no treatment were not included and thus contributed to the relatively low prevalence rate of bipolar disorder. Although the treated prevalence rate (0.5%) in this claim database analysis was somewhat lower than other estimates of the prevalence rate of bipolar disorder, it was consistent with previous estimates since it reflects an employed population, whereas national estimates typically include persons not in the workforce, among whom the rate of bipolar disorder may be higher.[1] Second, patients who may have bipolar disorder and received treatment other than antidepressants were also excluded from the final sample of 9009 patients. Therefore, it is difficult to generalize the results to recognized-BP patients, since some of the recognized-BP patients, for whom mood stabilizers are often initiated, were not included. However, similar analyses have demonstrated that bipolar patients utilized a greater amount of health care resources than randomly selected age- and sex-matched non-bipolar patients in a privately insured population[24] and that direct health care costs were significantly higher among patients who delayed or did not use mood stabilizers during their first year of bipolar disorder therapy.[13] Therefore, exclusion of these recognized-BP patients might have led to an overestimation of the utilization of health care resources by all bipolar disorder patients (including those with bipolar disorder treated both with and without antidepressants).

Because current evidence of the effects of antidepressants in bipolar disorder is inconclusive, further analyses comparing bipolar patients treated with and without antidepressants should be conducted to better understand the implication of antidepressant treatment for bipolar disorder. Despite these limitations, this study demonstrated that a substantial number of antidepressant-treated depressed patients could be classified as bipolar (either recognized-BP or unrecognized-BP) and were at risk for plausible induction of mania.

The key finding from the analysis of medication treatment patterns indicated that only 44% of recognized-BP patients used combination treatment for bipolar disorder and that an even smaller group of these patients (34%) were actually treated with antidepressants and mood stabilizers, as recommended by the current treatment guidelines.[30] In other words, over 50% of patients with recognized-BP were managed using antidepressant monotherapy, even though antidepressants, particularly tricyclics, are problematic because of their potential to induce hypomania or mania or to accelerate cycles. In this dataset, approximately 7.5% of bipolar patients met the criteria for plausible induction of mania. Therefore, much effort still needs to go toward translating practice guidelines into prescribing behavior to improve quality of care for bipolar disorder, particularly the depressive phase of bipolar disorder, in real world practice, in which pharmacotherapy often is done by "trial and error" and evidence about the individual's particular manifestation is frequently inferred from medication response.

The cost results demonstrate that while bipolar patients have greater expenditures than non-BP patients, recognition of bipolar disorder appears to reduce costs in the period subsequent to initiation of antidepressant therapy. The cost differences were largely due to the greater utilization of hospital services by unrecognized-BP patients than recognized-BP and non-BP patients. Generally, unrecognized-BP patients utilized more medical services than recognized-BP patients. One interpretation of this finding is that unrecognized-BP patients sought more medical services in an effort to diagnose and manage their bipolar condition, whereas recognized-BP patients had been trying to manage their bipolar disorder and had been seeking consistent treatment. Unrecognized-BP and recognized-BP patients appeared similar in terms of pharmacy costs, which may be due to the switching and augmenting practice in diagnosing and treating bipolar disorder.

In the 6 months prior to initiation of antidepressant therapy, recognized-BP patients had significantly higher costs than non-BP patients, due primarily to the expenses of their bipolar disorder treatment. Unrecognized-BP patient costs were not significantly different from recognized-BP patient costs, although the point estimate for unrecognized-BP patients was lower by $89 per month. Similarly, the point estimate for unrecognized-BP patient costs was higher (but not significantly) than that of non-BP patient costs (by $107). The absence of statistical significance in both of these comparisons may reflect the costs implicit in obtaining a correct diagnosis and the wide variance in the costs of the unrecognized-BP sample.

The sensitivity and implication of using an outcome measure such as monthly cost in the 12 months subsequent to initiation of antidepressant treatment was also addressed. Indeed, we investigated the monthly costs incurred in the 3 months after bipolar disorder diagnosis (irrespective of the timing of the index date) for recognized-BP and unrecognized-BP patients and found that unrecognized-BP patients had significantly greater monthly costs than recognized-BP patients ($1327 vs. $836) in this period. Unrecognized-BP patients appeared to experience more medical issues and require more maintenance therapy even after recognition of their bipolar disorder than recognized-BP patients. Further research could investigate this pattern.

Recognized-BP patients had a significantly higher rate of any mental illness during the 6 months prior to antidepressant therapy compared with non-BP and unrecognized-BP patients. Unrecognized-BP and non-BP patients had a similar rate, consistent with the belief that unrecognized-BP patients are often misdiagnosed with other mental illnesses prior to the recognition of bipolar disorder.[11] The results also suggested that recognized-BP patients specifically received treatment for their bipolar disorder and were hospitalized more frequently than unrecognized-BP patients and major depressive disorder patients.

For unrecognized-BP employees, monthly indirect (work loss) costs increased by 1.5 times in the 12 months after the antidepressant therapy initiation ($570) compared with the 6 months before ($371). Thus, work loss among unrecognized-BP active employees became more burdensome to the employer in the time after initiation of antidepressant therapy as the patients approached diagnosis and treatment of bipolar disorder. In the 12 months after initiation of antidepressant therapy, active employees with bipolar disorder incurred more than 1.5 times as many disability dollars as non-BP patients. This pattern is consistent with other findings that a high percentage of bipolar patients are unemployed after hospitalization for bipolar disorder.[25] While this analysis demonstrated the large work loss burden of bipolar disorder, indirect costs were underestimated in this analysis since sporadic sick time not related to disability or medical treatment was not captured. In addition, a greater percentage of bipolar patients than non-BP patients were early retirees, which suggests that bipolar disorder may lead to premature departure from the workplace.

Future research could investigate these treatment and cost patterns in a multivariate model to identify and

predict non-BP patients who may eventually become bipolar disorder patients. For example, patients classified as non-BP, recognized-BP, or unrecognized-BP have very different cost profiles in the prior 6 months than they do in the 12 months after initiation of antidepressant therapy. In part, this may reflect a pattern whereby the lack of recognition of bipolar disorder leads to less effective treatment for unrecognized-BP patients, which increases costs. We also recognize that prior use of health care services is a major predictor of future use, which suggests the need for a multivariate analysis. Since this research is meant to be suggestive, the underlying hypothesis about patterns of cost should be more fully addressed in future research. Analysis could also study the role of treatment history and comorbidities in the economic profile of bipolar disorder, as well as more fully address the impact of the timing of bipolar disorder diagnosis and of alternative treatments on patients' cost. From a policy perspective, these results suggest that more effort is needed to quickly diagnose and effectively treat bipolar patients.

## CONCLUSION

As compared with the recommendation from the American Psychiatric Association practice guidelines,[30] the medication treatment patterns for bipolar disorder were suboptimal in that antidepressant monotherapy predominated, particularly in unrecognized-BP patients. Although recognized-BP and unrecognized-BP patients initiated treatment with more combination therapies than non-BP patients and mood stabilizer use increased when bipolar disorder was recognized, a large proportion of bipolar disorder patients were treated with antidepressants alone. Bipolar disorder patients were costly to manage. In general, utilization of medical services was higher among bipolar patients, and those expenditures drove the costs of treating bipolar patients. Furthermore, compared with recognized-BP and non-BP patients, the economic burden of unrecognized-BP patients was more substantial. Therefore, accurate and timely recognition of bipolar disorder was associated with lower overall medical costs and lower indirect work loss.

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