Healthcare resource utilization, costs and treatment patterns in patients with bipolar disorder treated with lurasidone or cariprazine

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ABSTRACT

Objective: To compare healthcare resource utilization (HCRU), costs, and treatment adherence and persistence for patients with bipolar disorder treated with lurasidone or cariprazine.

Methods: Adult patients with bipolar disorder who initiated lurasidone or cariprazine as monotherapy or adjunctive therapy between 1 January 2016 and 30 June 2019 were identified from the IBM MarketScan Commercial and Medicare Supplemental Database. The date of the first claim for lurasidone or cariprazine was defined as the index date. A difference-in-difference (DID) analysis, which mitigated bias by using each cohort as its own control, compared the changes in HCRU and costs from 6-months pre-treatment (baseline) to 6-months post-treatment (follow-up) between the two cohorts. Treatment adherence (medication possession ratio and proportion of days covered) and persistence (time to discontinuation) were assessed during the 6-month post-treatment period. Adjusted analyses were conducted using inverse probability of treatment weighting on HCRU, costs, and time to discontinuation.

Results: A total of 16,683 patients treated with lurasidone and 4,128 patients treated with cariprazine were identified. Average age (39–40) and proportion female (68–71%) were similar between cohorts. Both cohorts had reductions in hospitalizations from baseline to follow-up, and the decrease was significantly greater for the lurasidone cohort compared to the cariprazine cohort (change in the proportion of patients with all-cause hospitalizations: −5.3% vs. −2.5%, DID = −2.8%, p < .001). The total healthcare costs increased from baseline to follow-up in both cohorts, and the increase was significantly lower for the lurasidone cohort compared to the cariprazine cohort (change in total all-cause healthcare cost per person: $3,413 vs. $4,642, DID = −$1,228, p < .001). The lurasidone cohort had significantly lower risk of discontinuing treatment (hazard ratio = 0.86, p < .001) than the cariprazine cohort.

Conclusions: Patients with bipolar disorder treated with lurasidone had greater reductions in hospitalizations from 6-months pre-treatment to 6-months post-treatment and had a lower increase in total costs compared to patients treated with cariprazine.

INTRODUCTION

Bipolar disorder is a chronic affective condition characterized by the presence of recurring manic or hypomanic episodes that alternate with depressive episodes. Bipolar I disorder is defined by at least one manic episode while bipolar II disorder is defined by at least one hypomanic episode. The depressive phase of bipolar disorder (bipolar depression) accounts for the majority (70%) of symptomatic time in bipolar I disorder and significantly impacts morbidity, mortality and disability. Bipolar depression is the main cause of psychosocial and occupational impairment in bipolar disorder.

The World Mental Health Survey Initiative estimated the lifetime prevalence of bipolar I disorder and bipolar II disorder to be 1.0% and 1.1%, respectively in the United States (US). Patients with bipolar disorder have decreased life expectancy and higher rates of cardiometabolic (e.g. cardiovascular disease, hypertension, diabetes) and psychiatric comorbidities (e.g. anxiety, substance abuse, personality disorder) compared to the general population.

The economic burden of bipolar disorder is substantial in the US. The annual total cost of bipolar disorder is over $195 billion of which approximately $155 billion can be attributed to indirect costs (e.g. unemployment, lost work productivity for patients/caregivers) and $40 billion to direct healthcare costs. Direct healthcare costs are driven, in part, by inpatient hospitalizations, which make up approximately 30% of the costs of treating patients with bipolar I disorder.

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Four atypical antipsychotics have been approved by the US Food and Drug Administration (FDA) for the treatment of adult patients with bipolar depression: lurasidone, cariprazine, quetiapine, and olanzapine/fluoxetine combination. Among these four, lurasidone is the only atypical antipsychotic approved as both monotherapy and adjunctive therapy with lithium or valproate for the treatment of major depressive episodes associated with bipolar I disorder in adults (both approved in June 2013). Cariprazine was initially approved for the treatment of manic or mixed episodes (approved in September 2015) and recently approved for the treatment of depressive episodes (approved in May 2019) associated with bipolar I disorder in adults. Lurasidone demonstrates high binding affinity for dopamine D2 and serotonin 5-HT2A and 5-HT7 receptors as an antagonist and moderate binding affinity for serotonin 5-HT1A receptors as a partial agonist. Cariprazine shows high binding affinity for dopamine D3, dopamine D2, and serotonin 5-HT2B receptors as a partial agonist and moderate affinity for serotonin 5-HT1A (partial agonist) and 5-HT2A (antagonist) receptors. Lurasidone’s antidepressant effects are believed to be mediated, in part, by 5-HT7 activity whereas potent binding to D3 is thought to be associated with cariprazine’s effect on mood.

Previous studies have compared hospitalization risks and treatment adherence for patients with bipolar disorder treated with lurasidone to other atypical antipsychotics using real-world data. However, there are no published studies comparing lurasidone and cariprazine on healthcare resource utilization, costs, and treatment patterns among patients with bipolar disorder. Lurasidone and cariprazine are the two most recently approved atypical antipsychotics for the treatment of bipolar depression and are both recommended as initial treatments for bipolar depression. This study evaluated real-world healthcare resource utilization, healthcare costs, and treatment patterns for patients with bipolar disorder treated with lurasidone or cariprazine.

Methods

Data source

The retrospective analysis used administrative claims from the IBM MarketScan Commercial and Medicare Supplemental Database (IBM Corporation; Somers, NY, USA) between 1 July 2015 and 31 December 2019. The MarketScan database includes over 40 million individuals annually and provides a nationally representative sample of the commercially insured population in the US. The database is constructed from de-identified patient-level medical claims, outpatient pharmacy claims, and enrollment data for individuals covered by employer-sponsored or Medicare-supplemental health insurance. The data include patient demographic characteristics, health plan enrollment information, inpatient and outpatient diagnoses and procedures, and prescription details as well as provider reimbursements, patient copayments, and deductible amounts for the services. The de-identified data are extracted in compliance with the Health Insurance Portability and Accountability Act of 1996. Therefore, institutional review board approval of this study was not required.

Patient selection

Patients with at least one prescription claim for lurasidone or cariprazine between 1 January 2016 and 30 June 2019 were eligible for inclusion in the study. The date of the first prescription fill of lurasidone or cariprazine was defined as the index date. Two study cohorts were constructed based on the index treatment. Patients could be treated with the index treatment (lurasidone or cariprazine) as monotherapy or adjunctive therapy. Patients were required to have continuous enrollment in a health insurance plan for 6 months before (baseline) and 6 months after the index date (follow-up).

Patients were included in the analysis if they were adults (age ≥18 years on the index date) and had ≥1 claim with a diagnosis of bipolar I disorder, other bipolar disorders, or unspecified bipolar disorder (International Classification of Diseases, 9th Revision, Clinical Modification codes [ICD-9-CM]: 296.0X, 296.1X, 296.4X, 296.5X, 296.6X, 296.7X, 296.80, 296.81, 296.89; 10th revision [ICD-10-CM]: F30.XX, F31.0, F31.1X, F31.2, F31.3X, F31.4, F31.5, F31.6X, F31.7X, F31.89, F31.9) during the study period. Patients with only a bipolar II disorder diagnosis code (ICD-10-CM: F31.81) were not included because both lurasidone and cariprazine are approved for the treatment of patients with depressive episodes associated with bipolar I disorder. A sensitivity analysis that included the bipolar II disorder diagnosis code was conducted. Patients were excluded from the analysis if they had ≥1 claim with a diagnosis of schizophrenia (ICD-9-CM: 295.xx, ICD-10-CM: F20.xx, F25.xx) in the 6-month baseline period or on the index date; had prescription claims for both lurasidone and cariprazine on the index date; or had a prescription claim for lurasidone (for cariprazine cohort) or cariprazine (for lurasidone cohort) during the baseline period.

Figure 1. Study design.
Study outcomes

All-cause and psychiatric-related HCRU and costs were calculated during the 6-months pre- and 6-months post-index periods for each cohort. HCRU and costs were reported for three categories: inpatient hospitalizations, outpatient visits, and pharmacy prescriptions. Outpatient visits were further categorized as emergency department (ED) visits, office visits, and other outpatient visits. No care settings were omitted. The number of outpatient visits was defined as the number of unique dates of service when a visit occurred. Psychiatric-related services included medical claims with a diagnosis code for a psychiatric condition in any diagnosis code field (Supplementary Materials Table S1) and pharmacy claims for treatments for psychiatric conditions (Supplementary Materials Table S2). Healthcare costs were inflated to 2019 US dollars using the annual medical care and drug costs components of the Consumer Price Index (CPI). To evaluate the changes in HCRU and costs following index treatment initiation, the difference between the pre- and post-index periods was calculated for each study measure for each cohort.

Treatment adherence was assessed for both cohorts during the 6-month follow-up period using the medication possession ratio (MPR) and proportion of days covered (PDC). MPR was calculated as the sum of the days supply for all prescription fills of the index treatment during the 6-month period divided by the number of days in the 6-month period. PDC was calculated as number of days that were covered by the index treatment during the 6-month period divided by the number of days in the 6-month period. The proportion of patients with MPR ≥75% and ≥80% and with PDC ≥75% and ≥80%, common definitions of adherence, during the 6-month follow-up period, were reported. Treatment persistence was assessed using time to discontinuation. Treatment discontinuation was defined as a gap of ≥45 days between the last day of the previous fill and the start date of the subsequent fill. The discontinuation date was recorded as the last day of supply of the index treatment (lurasidone or cariprazine) before the gap. Median time to discontinuation was estimated as days from index date to the time when 50% of population discontinued treatment. Switching was recorded for patients who switched from lurasidone to cariprazine or vice versa during the follow-up period, and those patients were considered to have discontinued the index treatment. Switching to other atypical antipsychotics was also considered discontinuation of the index treatment. The average dose of the index treatment was calculated over the treatment duration or the 6-month follow-up period, whichever was shorter, for both cohorts. The proportion of patients who switched treatment during the 6-month follow-up period was reported.

Demographics and baseline characteristics

Patient demographic characteristics (e.g. age, sex, geographic region) and dosage of index treatment were assessed at index date. Charlson comorbidity index calculated using the Quan method, cardiometabolic comorbidities (hypertension, type 2 diabetes mellitus, obesity, hyperlipidemia), psychiatric comorbidities (major depressive disorder [MDD], anxiety, personality disorder, substance use disorders), and concomitant medication use (antidepressant, anxiolytic, mood stabilizer, atypical antipsychotics other than lurasidone or cariprazine) were assessed during the 6-month baseline period. The use of the most frequently used atypical antipsychotics including aripiprazole, olanzapine, risperidone, and quetiapine during the baseline period was also reported. The bipolar disorder diagnosis type was determined based on the diagnosis codes observed. If patients had diagnosis codes for more than one type, they were classified using the following hierarchy: bipolar depression (ICD-9-CM: 296.5X; ICD-10-CM: F31.3X, F31.4, F31.5, F31.75, F31.76), bipolar mania (ICD-9-CM: 296.0X, 296.1X, 296.4X, 296.81; ICD-10-CM: F30.XX, F31.0, F31.1X, F31.2, F31.73, F31.74, F31.89), bipolar mixed (ICD-9-CM: 296.6X; ICD-10-CM: F31.6X, F31.77, F31.78), or unspecified (ICD-9-CM: 296.7X, 296.80, 296.89; ICD-10-CM: F31.70, F31.71, F31.72, F31.9)15.

Statistical analysis

All measures were reported with descriptive statistics using frequencies and percentages for categorical variables and mean and standard deviation (SD) for continuous variables. Statistical significance was tested using Chi-square tests for categorical variables and Student t-tests for continuous variables. A difference-in-difference (DID) analysis was conducted to compare the changes in all-cause and psychiatric-related HCRU and costs 6-month pre- and post-treatment between the lurasidone and cariprazine cohorts. DID analysis can mitigate bias related to unobserved and observed factors by using each cohort as its own control. Statistical significance was reported from bivariate (i.e. treatment cohort as the only covariate in the model) generalized linear models with a binomial distribution for categorical outcomes, a Poisson distribution for non-cost continuous outcomes, and a gamma distribution for costs. Propensity score weighted regression models with normalized inverse probability of treatment weighting (IPTW) were used to compare the HCRU, costs, and time to discontinuation for the lurasidone and cariprazine cohorts. The propensity score indicates a subject’s probability of receiving the treatment of interest conditional on observed covariates including age, sex, geographic region, payer type, bipolar disorder type, comorbidities (hyperlipidemia, obesity, substance abuse disorder, personality disorder, anxiety, major depressive disorder), and atypical antipsychotic use during the 6-month baseline period. Weighting subjects by the inverse probability of treatment received creates a synthetic sample in which treatment assignment is independent of observed baseline covariates. IPTW using the propensity score allows unbiased estimates of average treatment effects. This method was chosen over other methods (e.g. matching) to retain all subjects in the study sample.
Standardized differences before and after weighting were evaluated as a balance assessment of baseline covariates.

Two logistic regression models were developed to calculate the propensity of receiving cariprazine vs. lurasidone. The first model was used in the IPTW analyses for HCRU and costs and included the following covariates: age, sex, geographic region, payer type, bipolar disorder type, comorbidities, and atypical antipsychotic use during the 6-month baseline period. Baseline HCRU was not included as a covariate because it was adjusted for by the DID design. The second model was used in the Cox proportional hazards model with IPTW to examine time to discontinuation of index treatment. Covariates in the second model included all the covariates in the first model and hospitalization, ED visits, and total costs during the 6-month baseline period. Adjusted Kaplan Meier curves were plotted on time to discontinuation for both cohorts as well.

A sensitivity analysis was conducted that expanded the inclusion criteria to also include patients with ≥1 claim with a diagnosis of bipolar II disorder (ICD-10-CM: F31.81). All statistical analyses were performed using SAS version 9.4 (SAS Institute; Cary, NC, USA). Statistical significance was noted for all analyses at \( p < .05 \).

Results

Patient characteristics

The final sample included 16,683 patients in the lurasidone cohort and 4,128 patients in the cariprazine cohort (Figure 2). Table 1 shows the patient characteristics at the index date or during the baseline period.

The average age of the sample was similar between cohorts (39–40 years), and 68–71% were female. Commercial insurance was the predominant payer type in both cohorts (>95%), and less than 5% had Medicare Supplemental insurance. Almost half of the patients were from the South for both cohorts (44–52%), 21–22% from the Midwest, 17–19% from the Northeast, and 11–15% from the West.

Over half (51–56%) of patients had bipolar depression, 22–24% had unspecified bipolar, 13–16% had bipolar mania, and 7–11% had mixed bipolar for both cohorts. During the 6-month baseline period, 21–22% of patients had hypertension, 18–19% had hyperlipidemia, 17–19% had obesity, and approximately 14% had type 2 diabetes mellitus. Over half (55–57%) of patients had anxiety, 44–45% had MDD, and 23–25% had substance abuse disorders. Concomitant medications received by patients during the baseline period included antidepressants (68–69%), mood stabilizers (60%), atypical antipsychotics (51–59%), and anxiolytics (49–53%). At treatment initiation, the average doses were 47.7 mg per day for lurasidone and 2.4 mg per day for cariprazine.

A greater proportion of patients in the lurasidone cohort had at least one all-cause or psychiatric hospitalization during the 6-month baseline period compared to patients in the cariprazine cohort (all-cause: 21.5 vs. 14.0%, psychiatric-related: 19.9 vs. 12.6%, both \( p < .001 \)). During the 6-month baseline period, prior to initiating treatment with lurasidone, patients in the lurasidone cohort had higher inpatient costs (all-cause: $5,041 vs. $3,397, psychiatric-related: $3,776 vs. $2,335, both \( p < .001 \)) and total (all-cause: $15,143 vs. $12,432, psychiatric-related: $8,643 vs. $6,021, both \( p < .001 \)) healthcare costs compared to the cariprazine cohort.

Pre-post difference in HCRU

Table 2 shows the HCRU results for the 6-months pre- and post-treatment, the pre-post difference for each cohort, and the difference-in-difference results between the lurasidone and cariprazine cohorts. Figure 3 illustrates the difference-in-difference results for the proportion of patients with at least one hospitalization.

The proportion of patients with at least one hospitalization decreased from the 6-month baseline to 6-month follow-up period in both cohorts, and the decrease was significantly greater for the lurasidone cohort compared to the cariprazine cohort. For the lurasidone cohort, the decrease between 6-months pre- and post-treatment in the proportion of patients with at least one all-cause hospitalization was over two times greater than the decrease for the cariprazine cohort (-5.3 vs. -2.5%, DID = -2.8%, \( p < .001 \)). Similar results were found for psychiatric-related hospitalizations (-5.0 vs. -2.4%, DID = -2.7%, \( p < .001 \)). The all-cause and psychiatric average inpatient length of stay showed significantly greater decreases between 6-months pre- and post-treatment among patients in the lurasidone cohort compared to patients in the cariprazine cohort (all-cause: -0.54 vs. -0.25 days, DID = -0.29 days, \( p = .029 \); psychiatric-related: -0.52 vs. -0.26 days, DID = -0.27 days, \( p = .041 \)). The average number of hospitalizations followed a similar pattern between 6-months pre- and post-treatment (all-cause: -0.062 vs. -0.034, DID = -0.029, \( p = .016 \); psychiatric: -0.060 vs. -0.032, DID = -0.028, \( p = .013 \)).

The average number of outpatient office visits in both cohorts increased from the 6-month baseline to 6-month follow-up period, but the increase was significantly greater for the lurasidone cohort compared to the cariprazine cohort (all-cause: 0.56 vs. 0.25, \( D I D = 0.31 \), \( p < .001 \); psychiatric-related: 0.60 vs. 0.29, \( D I D = 0.30 \), \( p < .001 \)). The average number of other outpatient visits followed a similar pattern between 6-months pre- and post-treatment (all-cause: 1.46 vs. 0.66, \( D I D = 0.79 \), \( p < .001 \); psychiatric-related: 1.50 vs. 0.63, \( D I D = 0.87 \), \( p < .001 \)).

Pre-post difference in healthcare costs

Table 3 shows the healthcare costs for the 6-months pre- and post-treatment, the pre-post difference for each cohort, and the difference-in-difference results between the lurasidone and cariprazine cohorts.

In both cohorts, there was a decrease in average inpatient costs from the 6-month baseline to 6-month follow-up period. The reduction in average inpatient costs between 6-months pre- and post-treatment was greater for the lurasidone cohort compared to the cariprazine cohort (change in all-cause inpatient cost per person: -$1,052 vs. -$144,
Table 1. Baseline demographics and clinical characteristics for patients in the lurasidone cohort and cariprazine cohort.

|                               | Lurasidone cohort (N = 16,683) | Cariprazine cohort (N = 4,128) | p-Value |
|-------------------------------|-------------------------------|-------------------------------|---------|
| Age, mean (SD)                | 39.4 (14.4)                   | 40.0 (13.6)                   | .015    |
| Female, N (%)                 | 11,791 (70.7%)                | 2,818 (68.3%)                 | .002    |
| Payer type, N (%)             |                               |                               |         |
| Commercial                    | 16,054 (96.2%)                | 4,040 (97.9%)                 | <.001   |
| Medicare                      | 629 (3.8%)                    | 88 (2.1%)                     | <.001   |
| Geographic location, N (%)    |                               |                               |         |
| Northeast                     | 3,192 (19.1%)                 | 682 (16.5%)                   | <.001   |
| Midwest                       | 3,629 (21.8%)                 | 852 (20.6%)                   | .119    |
| South                         | 7,321 (43.9%)                 | 2,142 (51.9%)                 | <.001   |
| West                          | 2,466 (14.9%)                 | 445 (10.8%)                   | <.001   |
| Unknown                       | 55 (0.3%)                     | 7 (0.2%)                      | .091    |
| Average dose at treatment initiation, mg per day, mean (SD) | 47.7 (75.2) | 2.4 (2.6) | nr |
| Index medication pill strength |                               |                               |         |
| Lurasidone, N (%)             |                               |                               |         |
| 20 mg                         | 6,206 (37.2%)                 |                               | nr      |
| 40 mg                         | 5,903 (35.4%)                 |                               | nr      |
| 60 mg                         | 1,990 (11.9%)                 |                               | nr      |
| 80 mg                         | 1,858 (11.1%)                 |                               | nr      |
| 120 mg                        | 593 (3.6%)                    |                               | nr      |
| Mixed                         | 133 (0.8%)                    |                               | nr      |
| Cariprazine, N (%)            |                               |                               |         |
| 1.5 mg                        | 2,237 (54.2%)                 |                               | nr      |
| 3 mg                          | 1,562 (37.8%)                 |                               | nr      |
| 4.5 mg                        | 188 (4.6%)                    |                               | nr      |
| 6mg                           | 94 (2.3%)                     |                               | nr      |
| Mixed                         | 47 (1.1%)                     |                               | nr      |
| CCI score, mean (SD)          | 0.5 (1.1)                     | 0.4 (1.0)                     | .238    |
| Bipolar diagnosis type, N (%) |                               |                               |         |
| Bipolar depression            | 9,306 (55.8%)                 | 2,093 (50.7%)                 | <.001   |
| Bipolar mania                 | 2,248 (13.5%)                 | 674 (16.3%)                   | <.001   |
| Bipolar mixed                 | 1,183 (7.1%)                  | 446 (10.8%)                   | <.001   |
| Bipolar unspecified           | 3,946 (23.7%)                 | 915 (22.2%)                   | .043    |
| Psychiatric comorbidities, N (%)|                               |                               |         |
| Anxiety                       | 9,231 (55.3%)                 | 2,371 (57.4%)                 | .015    |
| Major depressive disorder     | 7,526 (45.1%)                 | 1,814 (43.9%)                 | .177    |
| Substance abuse disorders     | 4,196 (25.2%)                 | 958 (23.2%)                   | .010    |
| Personality disorder          | 1,054 (6.3%)                  | 227 (5.5%)                    | .050    |
| Cardiometabolic comorbidities, N (%)|                           |                               |         |
| Hypertension                  | 3,483 (20.9%)                 | 896 (21.7%)                   | .243    |
| Hyperlipidemia                | 2,935 (17.6%)                 | 798 (19.3%)                   | .009    |
| Obesity                       | 2,876 (17.2%)                 | 764 (19.0%)                   | .008    |
| Type 2 diabetes mellitus      | 2,282 (13.7%)                 | 568 (13.8%)                   | .892    |
| Concomitant medication, N (%) |                               |                               |         |
| Antidepressants               | 11,382 (68.2%)                | 2,863 (69.4%)                 | .162    |
| Mood stabilizers              | 10,069 (60.4%)                | 2,495 (60.4%)                 | .919    |
| Atypical antipsychotics       | 9,802 (58.8%)                 | 2,109 (51.1%)                 | <.001   |
| Anziprrolez                    | 2,605 (15.6%)                 | 811 (19.7%)                   | <.001   |
| Olanzapine                    | 1,037 (6.2%)                  | 317 (7.7%)                    | <.001   |
| Quetiapine                    | 2,910 (17.4%)                 | 793 (19.2%)                   | .008    |
| Risperidone                   | 928 (5.6%)                    | 249 (6.0%)                    | .242    |
| Anxiolytics                   | 8,100 (48.6%)                 | 2,197 (53.2%)                 | <.001   |
| All-cause HCRU and costs      |                               |                               |         |
| Proportion of patients with ≥1 hospitalization, N (%) | 3,584 (21.5%)                | 577 (14.0%)                   | <.001   |
| Inpatient costs, mean (SD)    | 5,041 (51.9%)                 | 3,397 (52.08%)                | <.001   |
| Total costs, mean (SD)        | $15,143 ($17,229)             | $12,432 ($30,076)             | <.001   |
| Psychiatric-related HCRU and costs |                               |                               |         |
| Proportion of patients with ≥1 hospitalization, N (%) | 3,327 (19.9%)                | 522 (12.6%)                   | <.001   |
| Inpatient costs, mean (SD)    | $3,776 ($13,451)              | $2,335 ($10,987)              | <.001   |
| Total costs, mean (SD)        | $8,643 ($18,719)              | $6,021 ($15,906)              | <.001   |

Abbreviations. CCI, Charlson Comorbidity Index calculated using Quan method; HCRU, healthcare resource utilization; mg, milligram; N, number of patients; nr, not reported.

DID = −$907, p = .033; psychiatric-related: −$945 vs. −$175, DID = −$770, p = .002. The lurasidone cohort had a lower increase in average pharmacy costs between 6-months pre- and post-treatment compared to the cariprazine cohort (change in all-cause pharmacy cost per person: $4,039 vs. $4,725, DID = −$685, p < .001; psychiatric-related: $3,894 vs. $4,453, DID = −$559, p < .001). Changes in outpatient costs from the 6-month baseline to 6-month follow-up period were similar across the lurasidone and cariprazine cohorts (change in all-cause outpatient cost per person: $426 vs. $61, DID = $365, p = .0174; psychiatric-related: $522 vs. $238, DID = $283, p = .073). The increase in average total healthcare costs was significantly lower between 6-months pre- and post-treatment for the lurasidone cohort compared to the cariprazine cohort (change in all-cause total costs per person: $3,413 vs. $4,642, DID = −$1,228, p = .022; psychiatric-related: $3,471 vs. $4,517, DID = −$1,046, p < .001).
Treatment adherence and persistence

Table 4 shows the treatment adherence and persistence results. Figure 4 shows the time to discontinuation of the index drug (lurasidone or cariprazine).

Compared to the cariprazine cohort, patients in the lurasidone cohort had a higher MPR (71 vs. 64%, p < .001) and a higher proportion of patients with MPR \( \geq 80\% \) (49 vs. 41%, p < .001) during the 6-month follow-up period. Similarly, patients in the lurasidone cohort had a higher PDC (62 vs. 57%, p < .001) and a higher proportion of patients with PDC \( \geq 80\% \) (44 vs. 36%, p < .001) during the 6-month follow-up period. Patients stayed on treatment with lurasidone longer than with cariprazine (median time to discontinuation = 129 days vs. 96 days, p < .001). The average dose of the index treatment over the treatment duration or the 6-month follow-up period, whichever was shorter, was 47.1 mg per day for lurasidone and 2.4 mg per day for cariprazine. During the
Table 2. All-cause and psychiatric-related healthcare resource utilization, unadjusted and adjusted difference-in-difference.

|                        | Lurasidone cohort | Cariprazine cohort | Unadjusted DID | p-Value | Adjusted DID | p-Value |
|------------------------|-------------------|--------------------|----------------|---------|--------------|---------|
|                        | 6-Month pre-index | 6-Month post-index | Pre-post difference | 6-Month pre-index | 6-Month post-index | Pre-post difference |
| **Inpatient hospitalization** |                   |                    |                 |         |              |         |
| Proportion of patients with ≥ 1 hospitalization, % | 21.5% | 16.2% | -5.3% | 14.0% | 11.4% | -2.5% | -2.8% | <.001 | -1.9% | .014 |
| Inpatient LOS, mean | 2.41 | 1.88 | -0.54 | 1.55 | 1.30 | -0.25 | -0.29 | .029 | -0.003 | .985 |
| Number of hospitalizations, mean | 0.305 | 0.242 | 0.062 | 0.196 | 0.163 | -0.034 | -0.029 | .016 | -0.015 | .267 |
| **Overall outpatient visits (inclusive of ED visits, office visits, and other outpatient visits)** |                   |                    |                 |         |              |         |
| Proportion of patients with ≥ 1 outpatient visit, % | 98.7% | 98.9% | 0.1% | 99.1% | 98.5% | -0.6% | 0.7% | .004 | 0.7% | .003 |
| Number of outpatient visits, mean | 19.67 | 21.61 | 1.94 | 19.36 | 20.23 | 0.87 | 1.07 | <.001 | 1.18 | <.001 |
| **Psychiatric-related** |                   |                    |                 |         |              |         |
| Proportion of patients with ≥ 1 hospitalization, % | 19.9% | 14.9% | -5.0% | 12.6% | 10.3% | -2.4% | -2.7% | <.001 | -1.8% | .015 |
| Inpatient LOS, mean | 2.29 | 1.77 | -0.52 | 1.48 | 1.22 | -0.26 | -0.27 | .041 | 0.03 | .883 |
| Number of hospitalizations, mean | 0.280 | 0.220 | -0.060 | 0.177 | 0.145 | -0.032 | -0.028 | .013 | -0.013 | .291 |
| **ED visits** |                   |                    |                 |         |              |         |
| Proportion of patients with ≥ 1 ED visit, % | 95.3% | 96.2% | 1.0% | 96.0% | 96.5% | 0.5% | 0.4% | .288 | 0.5% | .215 |
| Number of ED visits, mean | 6.42 | 6.98 | 0.56 | 6.78 | 7.03 | 0.25 | 0.31 | <.001 | 0.39 | <.001 |
| **Office visits** |                   |                    |                 |         |              |         |
| Proportion of patients with ≥ 1 office visit, % | 12.6% | 14.10 | 1.46 | 12.09 | 12.75 | 0.66 | 0.79 | <.001 | 0.76 | .002 |
| Number of office visits, mean | 14.82 | 17.44 | 2.62 | 15.71 | 18.60 | 2.89 | -0.27 | .025 | -0.01 | .915 |
| **Other outpatient visits** |                   |                    |                 |         |              |         |
| Proportion of patients with ≥ 1 other outpatient visit, % | 95.9% | 95.6% | -0.3% | 95.7% | 94.5% | -1.2% | 0.8% | .083 | 1.0% | .043 |
| Number of other outpatient visits, mean | 12.65 | 14.10 | 1.46 | 12.09 | 12.75 | 0.66 | 0.79 | <.001 | 0.76 | .002 |
| **Number of pharmacy prescriptions, mean** |                   |                    |                 |         |              |         |
| Proportion of patients with ≥ 1 pharmacy prescription, % | 93.8% | 94.0% | 0.2% | 95.4% | 94.1% | -1.3% | 1.5% | .001 | 1.6% | <.001 |
| Number of pharmacy prescriptions, mean | 6.42 | 6.98 | 0.56 | 6.78 | 7.03 | 0.25 | 0.31 | <.001 | 0.39 | <.001 |
| **Notes**: The adjusted DID model controlled for age, sex, geographic region, payer type, bipolar disorder type, comorbidities, and atypical antipsychotic use during the 6-month baseline period.
6-month follow-up period, 0.3% of patients in the lurasidone cohort switched to cariprazine, and 4.2% of patients in the cariprazine cohort switched to lurasidone.

**Adjusted analyses**

Differences in hospitalizations and healthcare costs were confirmed with adjusted analyses. After controlling for characteristics at the index date or baseline period, the reduction in the proportion of patients with all-cause and psychiatric-related hospitalizations between 6-months pre- and post-treatment remained significantly greater for the lurasidone cohort compared to the cariprazine cohort (all-cause: DID = −1.9%, p = .014; psychiatric-related: DID = −1.8%, p = .015; Table 2). The difference between 6-months pre- and post-treatment and between cohorts remained statistically significant for total costs (all-cause: DID = −$1,183, p = .038; psychiatric-related: DID = −$959, p = .007; Table 3) and pharmacy costs (all-cause: DID = −$670, p < .001; psychiatric-related: DID = −$546, p < .001; Table 3). Cox model results suggested that patients treated with lurasidone had a lower risk of discontinuing treatment during the 6-month follow-up period relative to patients treated with cariprazine (hazard ratio [HR] = 0.86, p < .001; Table 4). Balance assessment indicated that the two cohorts were well balanced after the IPTW weighting (Supplementary Materials Figure S3).

**Sensitivity analyses**

Results from the sensitivity analysis including patients with ≥1 claim with a diagnosis of bipolar II disorder were consistent with the primary analysis results. Compared to the cariprazine cohort (N = 4,484), the lurasidone cohort (N = 18,104) had a significantly greater reduction between 6-months pre- and post-treatment in the proportion of patients with at least one hospitalization (all-cause: −5.2 vs. −2.4%, DID = −2.8%, p < .001; psychiatric-related: −4.9 vs. −2.2%, DID = −2.7%, p < .001) and significantly lower increase in total healthcare costs (all-cause: $3,417 vs. $4,643, DID = −$1,226, p = .014; psychiatric-related: $3,483 vs. $4,535, DID = −$1,052, p < .001). In addition, patients in the lurasidone cohort had higher MPR (71 vs. 64%, p < .001) and PDC (62 vs. 57%, p < .001) during the 6-month follow-up period and longer treatment duration (median time to discontinuation = 127 days vs. 95 days, p < .001).
Figure 4. Adjusted Kaplan Meier curve for time to discontinuation. Notes: Covariates in the model included age, sex, geographic region, payer type, bipolar disorder type, comorbidities, atypical antipsychotic use, number of patients with inpatient hospitalizations, number of patients with ER visits, and total costs during the 6-month baseline period.

Discussion

This is the first real world study to compare HCRU, healthcare costs, and treatment patterns among patients receiving lurasidone or cariprazine for the treatment of bipolar disorder. Both cohorts had reductions in all-cause and psychiatric-related hospitalizations from 6-months pre-treatment to 6-months post-treatment, and the decrease was significantly greater for the lurasidone cohort compared to the cariprazine cohort. Although there was an increase in total healthcare costs during the 6-months post-treatment compared to the 6-months pre-treatment for both cohorts, patients treated with lurasidone had significantly lower increases in all-cause and psychiatric-related costs. Furthermore, patients treated with lurasidone had higher adherence and were less likely to discontinue treatment during the 6-month follow-up period than with cariprazine.

Our findings were consistent with previous studies comparing lurasidone with other oral atypical antipsychotics among patients with bipolar disorder. A retrospective database study using data from 2010 to 2014 reported that lurasidone-treated patients had lower hospitalization risks than other atypical antipsychotics (aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone) during 12 months of follow-up (hospitalization risk for other atypical antipsychotics vs. lurasidone, all-cause: odds ratio [OR] = 2.49–3.23; psychiatric-related: OR = 2.13–2.80)\textsuperscript{15}. A more recent study using data from 2014 to 2019 reported that lurasidone-treated patients had lower hospitalization risks than other atypical antipsychotics (aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone) during 12 months of follow-up (hospitalization risk for other atypical antipsychotics vs. lurasidone, all-cause: OR = 1.16–1.60; psychiatric-related: OR = 1.10–1.44) during 24 months of follow-up\textsuperscript{16}.

The findings that lurasidone had higher average MPR and PDC were also consistent with previous studies. A retrospective database study using data from 2009 to 2012 among patients with bipolar disorder who newly initiated atypical antipsychotic therapy reported that lurasidone had better adherence than other atypical antipsychotics (aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone) during 6 months of follow-up (lurasidone: mean MPR = 51–54%, other oral atypical antipsychotics: mean MPR = 42–52%)\textsuperscript{17}. Mean MPR for lurasidone-treated patients was higher in this study (68%) compared to the previous study (51–54%), which may be related to differences in study design such as including patients previously on atypical antipsychotic therapy and more recent data (2015–2019) in this study. Two adherence metrics (MPR and PDC) were reported in this study because both metrics have been shown to be good predictors of all-cause and mental health-related hospitalizations\textsuperscript{15}.

The results from this study demonstrated that patients treated with lurasidone had higher HCRU and costs during the baseline period, which suggests that lurasidone may have been utilized in a more difficult-to-treat population. This is consistent with results from a previous study, which reported that lurasidone-treated patients with bipolar disorder had a more complex clinical profile prior to initiating treatment with lurasidone compared to other oral atypical antipsychotics (aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone)\textsuperscript{16}. Therefore, a difference-in-difference design was used to control for potentially more clinically complex patients among the lurasidone cohort. The difference-in-difference design, which is commonly used in observational studies to measure treatment effect, allows for the comparison of outcomes, such as hospitalizations, before and after treatment and between groups while controlling for bias from unobserved and observed characteristics, such as disease severity, that vary between cohorts at baseline but remained fixed over time\textsuperscript{27–31}. If no relationship between treatment and hospitalizations is found, a DID estimate is equal to zero. An association between treatment and hospitalizations results in a DID estimate greater than or less than zero\textsuperscript{30,31}. The DID estimate for hospitalizations in this study was significantly less than zero, which indicates that patients treated with lurasidone, despite possibly greater clinical complexity at index, had significantly greater reductions in hospitalizations compared to patients treated with cariprazine.

The favorable HCRU and cost results for lurasidone compared to cariprazine in this study may be due, in part, to the potentially greater efficacy of lurasidone for the treatment of bipolar depression and higher adherence among the lurasidone cohort. Post-hoc analyses of clinical trials have shown that the rates of response and remission associated with lurasidone versus placebo may be numerically higher than cariprazine versus placebo\textsuperscript{37,38}. Higher adherence has been associated with fewer hospitalizations and ED visits and lower costs\textsuperscript{39–41}. In an exploratory analysis, we found that adherent patients (PDC $\geq$ 80%) were less likely to be hospitalized than non-adherent patients in this study population (12.1% of adherent patients vs. 17.5% of non-adherent patients; $p<.05$). Lurasidone has been shown to be well-tolerated in both short- and long-term trials (up to 2 years)\textsuperscript{42–45}, which could be a potential explanation for the higher adherence associated with lurasidone. It is worth noting that the rates of discontinuation due to adverse events were similar for lurasidone versus placebo and cariprazine versus placebo\textsuperscript{38}. More research is needed to explain the higher
adherence for the lurasidone cohort compared to the cariprazine cohort.

Total costs increased for both cohorts between the 6-month pre- and 6-month post-treatment periods, but the increase was lower in the lurasidone cohort. Patients in the lurasidone cohort had greater decreases in hospitalization costs, greater increases in outpatient costs, and smaller increases in pharmacy costs. The difference in the increases in total costs (adjusted, all-cause DID estimate = $1,183) was primarily driven by the greater reduction in hospital costs (adjusted, all-cause DID estimate = $848). The difference in pharmacy cost increases was likely due to other pharmaceuticals as the wholesale acquisition prices of lurasidone and cariprazine were similar at the time of the study.

Patients treated with lurasidone had a greater reduction in hospitalizations and greater increases in outpatient office and other non-ED outpatient visits between 6-months pre- and post-treatment. This suggests a larger shift from hospitalizations to office-based and other non-ED outpatient care compared to patients treated with cariprazine. This shift from inpatient to outpatient care could potentially indicate better care management. A previous study reported that outpatient follow-up care within 30 days of hospital discharge was associated with a lower hospital readmission risk among patients with bipolar disorder46.

There are several limitations to this study. First, administrative claims, which are commonly used for health services research, are collected for billing purposes and, therefore, may be subject to miscoding. Second, administrative claims do not capture all relevant clinical severity data, so disease severity could not be completely controlled for in this study. However, the difference-in-difference design mitigated any bias related to unobserved and observed factors by using each cohort as its own control. Third, this study is representative of a commercially insured population in the US but may not be generalizable to the uninsured, Medicare, and Medicaid populations. Fourth, patients were not required to stay on the index treatment during the 6-month follow-up period. However, this should have minimal impact on the findings because of very low switch rates (lurasidone to cariprazine = 0.3%; cariprazine to lurasidone = 4.2%). In addition, a previous open-label study reported that the effectiveness of lurasidone in adults with bipolar depression was maintained over a 6-month period45. Fifth, differences in the initial US FDA approvals for lurasidone (2010 for indication of schizophrenia and 2013 for indication of bipolar depression) and cariprazine (2015 for indication of schizophrenia and bipolar manic/mixed episode and 2019 for indication of bipolar depression) could lead to unknown bias. However, the bias should be minimized by the difference-in-difference design. Lastly, this study did not capture the differences in outcomes based on the use of the index treatments as monotherapy or adjunctive therapy.

Conclusions

Results from this retrospective database study suggest that patients with bipolar disorder treated with lurasidone had greater reductions in hospitalizations from 6-months pre-treatment to 6-months post-treatment and had lower increases in total costs compared to patients treated with cariprazine. Furthermore, patients treated with lurasidone were more adherent and less likely to discontinue treatment during the 6-month follow-up period than those treated with cariprazine.

Transparency

Declaration of funding

This study was funded by Sunovion Pharmaceuticals Inc.

Declaration of financial/other interests

H. Huang was an employee of Sunovion at the time of the study. Q. Fan, C. Dembek, G.R. Williams, and A. Loebel are employees of Sunovion. L. Schmerold and C. Dieyi are employees of STATinMED Research, which received funding from Sunovion to conduct this analysis.

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Author contributions

All authors were involved in the design of the study, data analysis, interpretation of results, drafting of the manuscript, and providing final review.

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Availability of data and material

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