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ORIGINAL RESEARCH

Real-World Disability Outcomes Among Patients Treated with Cariprazine vs Other Atypical Antipsychotics as Adjunctive Treatment for Major Depressive Disorder

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Purpose: Major depressive disorder (MDD) is a disabling condition that may require adjunctive treatment with atypical antipsychotics (AAs). However, little is known about how different adjunctive AAs impact disability outcomes. This analysis compared disability events, days, and costs among patients with MDD before and after initiating adjunctive treatment with cariprazine, brexpiprazole, or aripiprazole, which all belong to a class of AAs known as dopamine partial agonists.

Patients and Methods: The Merative™ MarketScan® Commercial Database and the Health and Productivity Management Database (1/1/2015-12/31/2022) were used to identify adults with MDD and ≥2 dispensings of cariprazine, brexpiprazole, or aripiprazole (first dispensing=index) adjunctive to antidepressant therapy. Baseline characteristics between cohorts were balanced using inverse probability of treatment weighting. Changes (post-index minus pre-index) in all-cause and mental health (MH)-related disability claim rates, days, and costs were compared for cariprazine vs brexpiprazole and cariprazine vs aripiprazole via a difference-in-difference analysis; 95% CIs were generated using nonparametric bootstrap procedures. *P*-values <0.05 were considered statistically significant.

Results: In the cariprazine (n=224) vs brexpiprazole (n=643) analysis, the cariprazine cohort had significantly greater reductions in all-cause disability claims, days, and costs vs the brexpiprazole cohort (between-cohort difference: −0.23 claims [*P*<0.05], −25.27 days [*P*<0.001], −$4577.08 [*P*<0.01], respectively). The cariprazine cohort also had a significantly greater reduction in MH-related disability days (−12.07 [*P*<0.05]); reductions in MH-related disability claims and mean costs vs brexpiprazole were similar. In the cariprazine (n=174) vs aripiprazole (n=2931) analysis, a significantly greater reduction for cariprazine vs aripiprazole was observed for all-cause and MH-related disability costs (all-cause: −$3275.91 [*P*<0.01]; MH-related: −$2196.36 [*P*<0.05]); reductions in all-cause and MH-related disability claims and days were similar.

Conclusion: In this real-world analysis of patients with MDD using AAs adjunctively to antidepressants, significantly greater reductions were observed in disability claims and days for cariprazine vs brexpiprazole and in disability costs for cariprazine vs aripiprazole. These results suggest that adjunctive cariprazine may have beneficial effects on disability outcomes for patients with MDD.

Plain Language Summary: Major depressive disorder (MDD) can lead to disability. Medications such as cariprazine, brexpiprazole, and aripiprazole can be used with antidepressants to treat MDD. This study compared the changes in disability outcomes in adults with MDD based on which of these medications they took with their antidepressant. Using insurance databases, we found patients with MDD using medications with antidepressants. We then looked at how disability outcomes changed from before to after starting treatment with different medications. We looked at disability events, or health events which required filing for disability. We also looked at the number of days on disability and the cost of disability. We compared before and after changes between cariprazine vs brexpiprazole and cariprazine vs aripiprazole. Compared with patients using brexpiprazole, patients using cariprazine had greater reductions in disability events, days, and costs. Patients using cariprazine vs brexpiprazole also had a greater reduction in disability

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days associated with mental health reasons specifically. Disability events and costs for mental health reasons were similar. For cariprazine vs aripiprazole, changes in disability events and days were similar. Changes in disability events and days for mental health-related reasons were also similar. Patients using cariprazine had a greater reduction in overall and mental health-related disability costs than patients using aripiprazole. Our results suggest that in patients with MDD, cariprazine with antidepressants had a greater benefit on disability outcomes than aripiprazole or brexpiprazole with antidepressants. This study was limited by the type of data available and smaller numbers of patients.

Keywords: cariprazine, major depressive disorder, disability, brexpiprazole, aripiprazole, adjunctive therapy

Introduction

Major depressive disorder (MDD) is a leading cause of disability worldwide,[1] with results of the 2019 National Health and Wellness Survey showing that 8.8% of respondents with MDD reported short- or long-term disability relative to 1.7% of respondents without MDD.[2] The negative effects of MDD are further reflected in its large, increasing economic burden. According to an analysis based on National Survey on Drug Use and Health estimates, the economic burden of MDD increased by 37.9% from $236.6 billion in 2010 to $333.7 billion in 2019 ($382.4 billion in 2023 US dollars [USD]).[3,4] The largest contributor to the growing economic burden of MDD from 2010 to 2018 was the 73.2% observed increase in workplace costs, which includes costs related to disabilities. Because steady employment in individuals with mental illness has been associated with decreased outpatient service use and healthcare costs relative to patients without steady employment,[5] decreased rates of disability may benefit not only patients but also payers. As >80% of adults with depression report difficulty with work and other daily activities owing to their symptoms,[6] effective treatment is imperative to decreasing the personal and economic burden of the disease. However, despite the substantial economic burden and associated workplace costs attributable to MDD, disability outcomes have not been well studied in the MDD population.

The episodic or relapsing nature of MDD can contribute to its negative impact on patients, including function and disability.[7–9] Because of this, the American Psychiatric Association recommends maintenance treatment with antidepressant therapy (ADT) for at least 4 months after successful treatment in the acute phase of the illness, with a longer duration of therapy recommended for patients who have a high risk of recurrent depressive episodes.[10] However, ~50% of patients with MDD experience inadequate response to first-line ADT.[11] For patients who do not respond to their initial ADT, 1 guideline-recommended treatment option is the addition of an atypical antipsychotic (AA) as an adjunct to ADT.[10,12,13] Adjunctive treatment with AAs has demonstrated efficacy vs placebo for the treatment of MDD in meta-analyses of clinical trial data[14,15] and has the benefit of allowing patients to remain on their initial ADT if they experienced a partial response.[16–18] Additionally, the use of adjunctive AAs has been associated with decreased healthcare resource utilization and healthcare costs. For instance, a claims-based analysis of adults with MDD found that the initiation of adjunctive AA treatment was associated with significantly decreased rates of all-cause and MDD-related hospitalizations and emergency department (ED) visits in the 12 months following adjunctive AA initiation compared with the 12 months before initiation.[19] Furthermore, another claims-based analysis of patients with MDD found that patients who initiated an AA as their first adjunctive therapy had significantly less healthcare resource utilization and lower total healthcare costs relative to patients who initiated an AA as their subsequent adjunctive therapy.[20] These prior analyses suggest that early initiation of adjunctive AAs for appropriate patients may result in decreased healthcare resource utilization and healthcare costs.

Currently, there are several AAs approved by the US Food and Drug Administration (FDA) for the adjunctive treatment of MDD, including aripiprazole, brexpiprazole, and cariprazine, which are part of a class of AAs known as dopamine partial agonists. Dopamine partial agonists are of interest because they are generally well tolerated, cause little sedation, are prolactin sparing, and have a low risk of weight gain.[21] Specifically, aripiprazole is a dopamine D_2 and serotonin $5HT_{1A}$ receptor partial agonist and serotonin $5HT_{2A}$ receptor antagonist that was approved by the FDA for the adjunctive treatment of MDD in 2007.[22] Brexpiprazole, which was approved for the adjunctive treatment of MDD in 2015, is a dopamine D_2 and D_3 receptor partial agonist that displays greater affinity for serotonin $5HT_{1A}$/$5HT_{2A}$ receptors

and α_{1B}-adrenergic receptors than aripiprazole.[23] The latest AA approved in 2022 for the adjunctive treatment of MDD is cariprazine,[24] which is a dopamine D_3-preferring D_3/D_2 and serotonin 5-HT_{1A} receptor partial agonist that has a longer half-life and higher relative affinity for the D_3 receptor compared with aripiprazole and brexpiprazole.[24,25] Although aripiprazole, brexpiprazole, and cariprazine have all demonstrated efficacy as dopamine partial agonists for the adjunctive treatments for MDD in clinical trial settings,[26–28] little is known about how they compare in terms of their real-world effects on disability outcomes.

Because MDD is associated with a substantial impact on workplace productivity and functionality,[29,30] evaluating the effects of different adjunctive AAs on disability outcomes is important to gain an overall understanding of the impacts of these medications. Although previous studies have shown a decreased rate of disability in patients with MDD treated with AAs adjunctive to ADTs,[31,32] these previous clinical trials generally used patient-reported outcomes to evaluate disability such as the Sheehan Disability Scale. Conversely, claims-based analyses of disability data can provide a view of the real-world effects of medications on disability outcomes. However, little is known about the real-world implications of AAs on disability outcomes. A previous analysis of disability outcomes using claims data before and after cariprazine initiation found that rates of all-cause and mental health (MH)-related disability claims, days, and costs were significantly lower after cariprazine initiation compared with before cariprazine treatment.[33] Nevertheless, the real-world disability outcomes associated with cariprazine compared with other adjunctive dopamine partial agonist AAs, as well as the costs associated with disability among various adjunctive AAs, remains unknown. Therefore, the goal of this analysis was to compare changes in all-cause and MH-related disability claims, days, and costs before and after treatment initiation with cariprazine vs brexpiprazole and cariprazine vs aripiprazole, among patients with MDD using AAs adjunctively to antidepressants.

Materials And Methods

Data Source and Study Design

This was a retrospective, observational cohort study using de-identified data from the Merative™ MarketScan® Commercial Database and the Health and Productivity Management (HPM) Database (January 1, 2015, to December 31, 2022).[34] The commercial database includes enrollment history and claims for medical and pharmacy services for patients from approximately 100 large-scale employers as well as several health plans. The HPM database includes integrated disability data for almost 3 million employees including enrollment in disability insurance plans and short- and long-term disability claims filed by patients with disability insurance, with data provided from employer payroll systems and disability case records by data contributors to the MarketScan Commercial Database. The data are fully linkable to the corresponding medical, pharmacy, and enrollment data for these employees. Details regarding the specific causes of disability are not available in the database, but disability claim records include medical diagnoses associated with the claim. All data are de-identified and compliant with the Health Insurance Portability and Accountability Act; therefore, no institutional review board was required.

The database was used to identify patients diagnosed with MDD who initiated adjunctive treatment with cariprazine, brexpiprazole, or aripiprazole, with the first dispensing defined as the index date (Figure 1). Patient demographics, clinical characteristics, and pre-index disability outcomes were evaluated during the baseline period, which spanned 12 months prior to the index date. Post-index disability outcomes were evaluated during the follow-up period, which was ≥30 days and lasted until the earliest date of the following: 1 year post-index, end of HPM or health insurance eligibility, diagnosis of schizophrenia or schizoaffective disorder, claim for a non-index AA, discontinuation of the index AA or ADT, or end of data availability.

Study Population

The analysis included adults (≥18 years old) with ≥2 dispensings of cariprazine, brexpiprazole, or aripiprazole. Separate analyses were conducted to compare cariprazine vs brexpiprazole and cariprazine vs aripiprazole. Evidence of adjunctive therapy with the index AA was required, defined as ≥1 ADT prescription within 90 days before the index date and an overlap of ≥30 days of supply of 1 ADT and the index AA during the 90 days post-index (Supplementary Table 1).

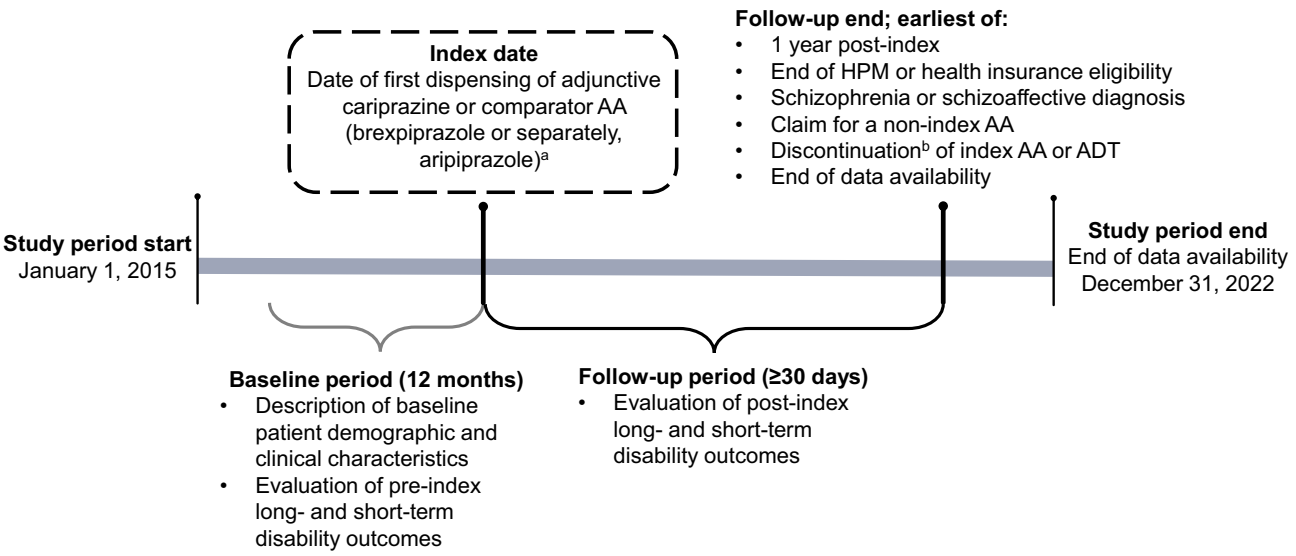

Figure 1 Study Design.
Notes: [a]Patients newly initiated on cariprazine or brexpiprazole were identified in the cariprazine vs brexpiprazole comparison (and similarly for the cariprazine vs aripiprazole comparison). [b]Discontinuation was defined based on a gap of >90 days in days of supply between the end of a dispensing and the next fill or between the last dispensing and the end of the follow-up period.
Abbreviations: AA, atypical antipsychotic; ADT, antidepressant therapy; HPM, Health and Productivity Management.

Patients were also required to have ≥30 days of follow-up after the index date and ≥12 months of continuous medical, pharmacy, and disability insurance coverage prior to the index date. The study included patients with a confirmed diagnosis of MDD within the 12 months before or on the index date, defined as ≥1 diagnosis in an inpatient setting or ≥2 diagnoses in an outpatient setting (Supplementary Table 2). Patients were excluded from the analysis if they had ≥1 diagnosis of bipolar I disorder, schizophrenia, or schizoaffective disorder during baseline or on the index date. In aiming to isolate our findings to the effects of the AAs of interest opposed to other treatments for major depressive disorder, patients were also excluded from the analysis if they had ≥1 dispensing for a non-index AA or mood stabilizer on the index date.

Study Outcomes

Outcomes included per patient-year (PPY) rates of all-cause and MH-related disability claims and days during baseline and follow-up. Between-cohort differences in means were used to compare the rates of claims and days PPY between adjunctive cariprazine vs adjunctive brexpiprazole and adjunctive cariprazine vs adjunctive aripiprazole. Disability claims and days were considered MH-related if the claim contained a primary or secondary MH diagnosis code. Disability days were measured as the total number of workdays spanned by all short- and long-term disability claims. All disability claims that started on or before the index date were considered baseline disability claims, whereas claims that started after the index date were considered follow-up disability claims.

In addition, all-cause and MH-related disability costs PPY during the baseline and follow-up period were evaluated, with between-cohort differences in means used to compare adjunctive cariprazine vs adjunctive brexpiprazole and adjunctive cariprazine vs adjunctive aripiprazole. When data were available, disability costs were measured using the costs reported on the disability case records. If the cost variable was missing, disability costs were estimated based on the number of short- and long-term disability days, median daily earnings rate (estimated using a median hourly wage of $22.26 based on the May 2022 National Occupational Employment and Wage Estimates for all occupations from the US Bureau of Labor Statistics),[35] and earnings replacement rate while on disability. Based on data from the US Bureau of Labor Statistics, the earnings replacement rate was assumed to be 60%.[36] Costs were adjusted to 2022 USD using the US hourly compensation price index.[35] The imputation of missing or zero costs was performed separately for MH-related and non–MH-related costs; all-cause costs were then calculated as the sum of MH-related and non–MH-related costs, whether imputed or available.

Statistical Analysis

Patients were assigned to mutually exclusive cohorts based on their index AA, and 2 separate pairwise comparisons were evaluated: 1) adjunctive cariprazine vs adjunctive brexpiprazole and 2) adjunctive cariprazine vs adjunctive aripiprazole. Inverse probability of treatment weighting (IPTW) based on the propensity score was used to balance baseline characteristics between patients in the adjunctive cariprazine and adjunctive comparator AA cohorts (brexpiprazole or aripiprazole). Variables used in the propensity score included age at index date, sex, geographic region, year of index date, physician specialty around index date, baseline Quan-Charlson Comorbidity Index (CCI) score, baseline MDD severity, baseline MH-related therapy use, baseline other supportive therapy use, baseline all-cause healthcare resource utilization (hospitalizations, ED visits, outpatient visits), baseline all-cause medical costs, and baseline comorbidities. Comorbidities included in the propensity score were *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (DSM-5) and Elixhauser comorbidities with a standardized difference (std diff) >10% between unweighted AA cohorts and a prevalence in the cariprazine cohort ≥5%. The weight was trimmed at 99th percentile of the distribution.

Patient demographics and clinical characteristics were analyzed using descriptive statistics, including mean, SD, and median values for continuous variables and relative frequencies and proportions for categorical variables. Differences in baseline characteristics between the unweighted AA cohorts were analyzed using std diff; variables with a std diff >10% were considered imbalanced.

A difference-in-difference analysis using a doubly robust approach, in which baseline patient characteristics that remained imbalanced after IPTW were included as covariates in the regression model, was used to compare mean changes in disability outcomes from baseline between the cariprazine and comparator AA cohorts. Specifically, the weighted pre-post difference in PPY disability outcomes for cariprazine was compared with brexpiprazole and aripiprazole (separately) and variables that remained imbalanced after weighting were included as regressors. Generalized linear models with an identity link were used to model the differences between outcomes in pre- and post-AA initiation periods for all outcomes. Statistical significance was determined using *P* values and 95% CIs, which were calculated using nonparametric bootstrap procedures with 499 resamples. *P* values <0.05 were considered statistically significant.

Results

Adjunctive Cariprazine vs Adjunctive Brexpiprazole

A total of 867 patients were included in the adjunctive cariprazine vs adjunctive brexpiprazole analysis, with 224 patients in the cariprazine cohort and 643 patients in the brexpiprazole cohort. After IPTW, the average age was 45–46 years, 62%-64% of patients were female, and the majority (73%-77%) of patients had a comorbid anxiety disorder (Table 1; Supplementary Tables 3 and 4). The average length of follow-up in the weighted cariprazine and brexpiprazole cohorts was approximately 4 months.

Table 1 Baseline Demographics and Clinical Characteristics: Adjunctive Cariprazine Vs Adjunctive Brexpiprazole

Characteristic	Weighted Cohorts[a]		Std diff[b] (%)
	Adjunctive Cariprazine (n=224)	Adjunctive Brexpiprazole (n=643)	
Age, mean (SD), y	45.4 (9.5)	45.7 (9.6)	3.1
Female, n (%)	143 (63.7)	398 (61.9)	3.8
Geographic region, n (%)			
Midwest	68 (30.3)	176 (27.4)	6.5
Northeast	17 (7.5)	56 (8.7)	4.5
South	106 (47.3)	313 (48.6)	2.5
West	26 (11.4)	83 (12.9)	4.6
Unknown	8 (3.4)	15 (2.4)	6.4

(*Continued*)

Table 1 (Continued).

Characteristic	Weighted Cohorts[a]		Std diff[b] (%)
	Adjunctive Cariprazine (n=224)	Adjunctive Brexpiprazole (n=643)	
Physician specialty at index,[c] n (%)			
Primary care	81 (36.4)	227 (35.2)	2.4
MH specialist	125 (55.7)	368 (57.2)	3.1
Other provider type	16 (7.4)	40 (6.2)	4.5
Missing	1 (0.6)	9 (1.4)	7.5
Quan-CCI,[d] mean (SD)	0.54 (1.21)	0.49 (1.00)	4.3
Top baseline DSM-5 comorbidities,[d] n (%)			
Anxiety disorders	172 (76.9)	471 (73.3)	8.3
Sleep-wake disorders	92 (40.9)	221 (34.4)	13.3
Trauma- and stressor-related disorders	54 (24.3)	169 (26.2)	4.4
Bipolar and related disorders	36 (15.9)	93 (14.4)	4.2
Substance-related and addictive disorders	44 (19.7)	126 (19.5)	0.3
Baseline MH medication use,[d,e] n (%)			
Adjunctive AAs (excluding index AA)	99 (44.1)	274 (42.7)	2.8
Mood stabilizers	5 (2.4)	6 (0.9)	11.6
Thyroid hormone	2 (0.8)	8 (1.2)	4.9
Other adjunctive therapies	35 (15.8)	104 (16.2)	1.2

Notes: [a]Cohorts were weighted using IPTW based on propensity scores. Variables used in the propensity score calculation included age at index date, sex, geographic region, year of index date, physician specialty around index, baseline Quan-CCI score, baseline MDD severity, baseline MH-related therapy use, baseline other supportive therapy use, other MH-related therapy used during baseline, baseline all-cause healthcare resource utilization (hospitalizations, ED visits, outpatient visits), baseline all-cause medical costs, and DSM-5 and Elixhauser comorbidities with std diffs >10% and a prevalence in cariprazine cohort ≥5%. The weight was trimmed at 99% of the distribution. Counts are rounded to the nearest integer, while percentages are calculated from continuous weighted values.[b]For continuous variables, the std diff is calculated by dividing the absolute difference in means of the control and the case by the pooled SD of both groups. The pooled SD is the square root of the average of the squared SDs. For dichotomous variables, the std diff is calculated using the following equation where P is the respective proportion of participants in each group: $|(Pcase–Pcontrol)| / \sqrt{[(Pcase(1–Pcase)+Pcontrol(1–Pcontrol))/2]}$.[c]Evaluated during the 45 days pre-index and 15 days post-index. MH specialists included psychiatrist, psychologist, psychiatric nurse, and child psychiatrist. Primary care physicians included family practice, internal medicine, pediatrician, hospitalist, multispecialty physician group, medical doctor, nursing services, and nurse practitioner. For patients with claims for both primary care physicians and MH specialists, physician type was classified as specialist. Patients with claims with a nonmissing provider type that did not belong to any of the other categories were classified as other provider type (not elsewhere classified).[d]Evaluated during the 12-month baseline period, excluding the index date.[e]Per study design, all patients were prescribed ≥1 ADT during the baseline period.

Abbreviations: AA, atypical antipsychotic; ADT, antidepressant therapy; CCI, Charlson Comorbidity Index; DSM-5, *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition*; ED, emergency department; IPTW, inverse probability of treatment weighting; MH, mental health; MDD, major depressive disorder; std diff, standardized difference.

For adjunctive cariprazine users, all-cause disability claims were 0.49 per patient-year (PPY) during the baseline period and 0.28 PPY during follow-up, while for adjunctive brexpiprazole users, all-cause disability claims were 0.44 PPY during the baseline period and 0.43 PPY during follow-up (Table 2); the reduction in all-cause disability claims was significantly greater in patients using adjunctive cariprazine compared with those using adjunctive brexpiprazole (adjusted between-cohort difference in means [95% CI]: −0.23 [−0.45, −0.02], P=0.028; Figure 2A). The rate of MH-

Table 2 Frequency and Rates of Short- and Long-Term Disability Outcomes: Adjunctive Cariprazine Vs Adjunctive Brexpiprazole

Short- and Long-Term Disability Outcomes	Frequency		Baseline Rate (PPY)		Follow-Up Rate (PPY)	
	Adjunctive Cariprazine	Adjunctive Brexpiprazole	Adjunctive Cariprazine	Adjunctive brexpiprazole	Adjunctive cariprazine	Adjunctive Brexpiprazole
Number of eligible patients	224	643	–	–	–	–
Follow-up period,[a] mean ± SD, y	0.33±0.21	0.37±0.22	–	–	–	–

(*Continued*)

Table 2 (Continued).

Short- and Long-Term Disability Outcomes	Frequency		Baseline Rate (PPY)		Follow-Up Rate (PPY)	
	Adjunctive Cariprazine	Adjunctive Brexpiprazole	Adjunctive Cariprazine	Adjunctive brexpiprazole	Adjunctive cariprazine	Adjunctive Brexpiprazole
Disability claims						
All-cause	27	89	0.49	0.44	0.28	0.43
MH–related[b]	11	42	0.25	0.21	0.10	0.21
Disability days						
All-cause	1150	6751	32.68	28.52	11.64	33.05
MH–related[b]	463	3432	19.53	16.15	4.22	14.54
Disability costs (2022 USD)[c]						
All-cause	–	–	$6427.16	$6077.80	$1637.74	$6009.26
MH–related[b]	–	–	$3700.61	$4179.48	$587.08	$2889.38

Notes: [a]The follow-up period spans from the index date to the earliest of 1 year post-index, end of HPM or health insurance eligibility, diagnosis of schizophrenia or schizoaffective disorder, claim for a non-index AA, discontinuation of AA or ADT, or end of data availability.[b]MH–related disability was defined as events with a primary or secondary MH diagnosis code.[c]Disability costs were defined as the sum of short- and long-term disability costs. If disability payments were zero or unavailable for a patient, they were estimated based on the number of disability days, median daily earnings rate (estimated using a median hourly wage of $22.26 based on the May 2022 National Occupational Employment and Wage Estimates for all occupations from the US Department of Labor Bureau of Labor Statistics), and earnings replacement rate of 60%. Costs were adjusted to 2022 USD using the US hourly compensation price index. The imputation of missing or zero costs was performed separately for MH-related and non–MH-related costs. Where either component was imputed, all-cause costs were calculated as the sum of MH-related and non–MH-related costs, whether imputed or available.

Abbreviations: AA, atypical antipsychotic; ADT, antidepressant therapy; HPM, Health and Productivity Management Database; MH, mental health; PPY, per patient-year; USD, US dollar.

related disability claims PPY in the adjunctive cariprazine cohort was 0.25 PPY during baseline and 0.10 PPY during follow-up, whereas the rate in the adjunctive brexpiprazole cohort was 0.21 PPY both before and after starting adjunctive treatment. However, the reduction in MH-related disability claims PPY was not significantly greater in the adjunctive cariprazine cohort relative to the adjunctive brexpiprazole cohort (−0.14 [−0.30, 0.01], P=0.068).

In the adjunctive cariprazine cohort, the rate of all-cause disability days was 32.68 PPY during the baseline period and 11.64 PPY during follow-up. In the adjunctive brexpiprazole cohort, the baseline rate was 28.52 PPY and the follow-up rate was 33.05 PPY. There was a statistically significantly greater reduction in all-cause disability days PPY for adjunctive cariprazine relative to adjunctive brexpiprazole (adjusted between-cohort difference in means [95% CI]: −25.27 [−41.62, −9.69], P<0.001; Figure 2B). Additionally, the rate of MH-related disability days PPY in the adjunctive cariprazine cohort was 19.53 PPY during the baseline period and 4.22 PPY during follow-up, while the rate in the adjunctive brexpiprazole cohort was 16.15 PPY during the baseline period and 14.54 PPY during follow-up; there was a statistically significantly greater reduction for adjunctive cariprazine relative to adjunctive brexpiprazole (−12.07 [−25.83, −0.62], P=0.032).

Among adjunctive cariprazine users, all-cause baseline disability costs (2022 USD) were $6427.16 PPY during the baseline period and $1637.74 PPY during follow-up. Among adjunctive brexpiprazole users, all-cause disability costs PPY were $6077.80 during baseline and $6009.26 during follow-up. A statistically significantly greater reduction in disability costs was observed for adjunctive cariprazine vs adjunctive brexpiprazole (adjusted between-cohort difference in means [95% CI]: −$4577.08[−8951.69, −786.37], P=0.004; Figure 2C). MH-related disability costs PPY for adjunctive cariprazine users were $3700.61 and $587.08 during baseline and follow-up, respectively, and for adjunctive brexpiprazole users were $4179.48 and $2889.38, respectively. The reduction estimate was similar for adjunctive cariprazine relative to adjunctive brexpiprazole (−$1670.36 [−4407.37, 748.84], P=0.20).

Adjunctive Cariprazine vs Adjunctive Aripiprazole

The adjunctive cariprazine vs adjunctive aripiprazole analysis included 3105 patients, with 174 patients included in the cariprazine cohort and 2931 patients included in the aripiprazole cohort. After IPTW, the average age was approximately

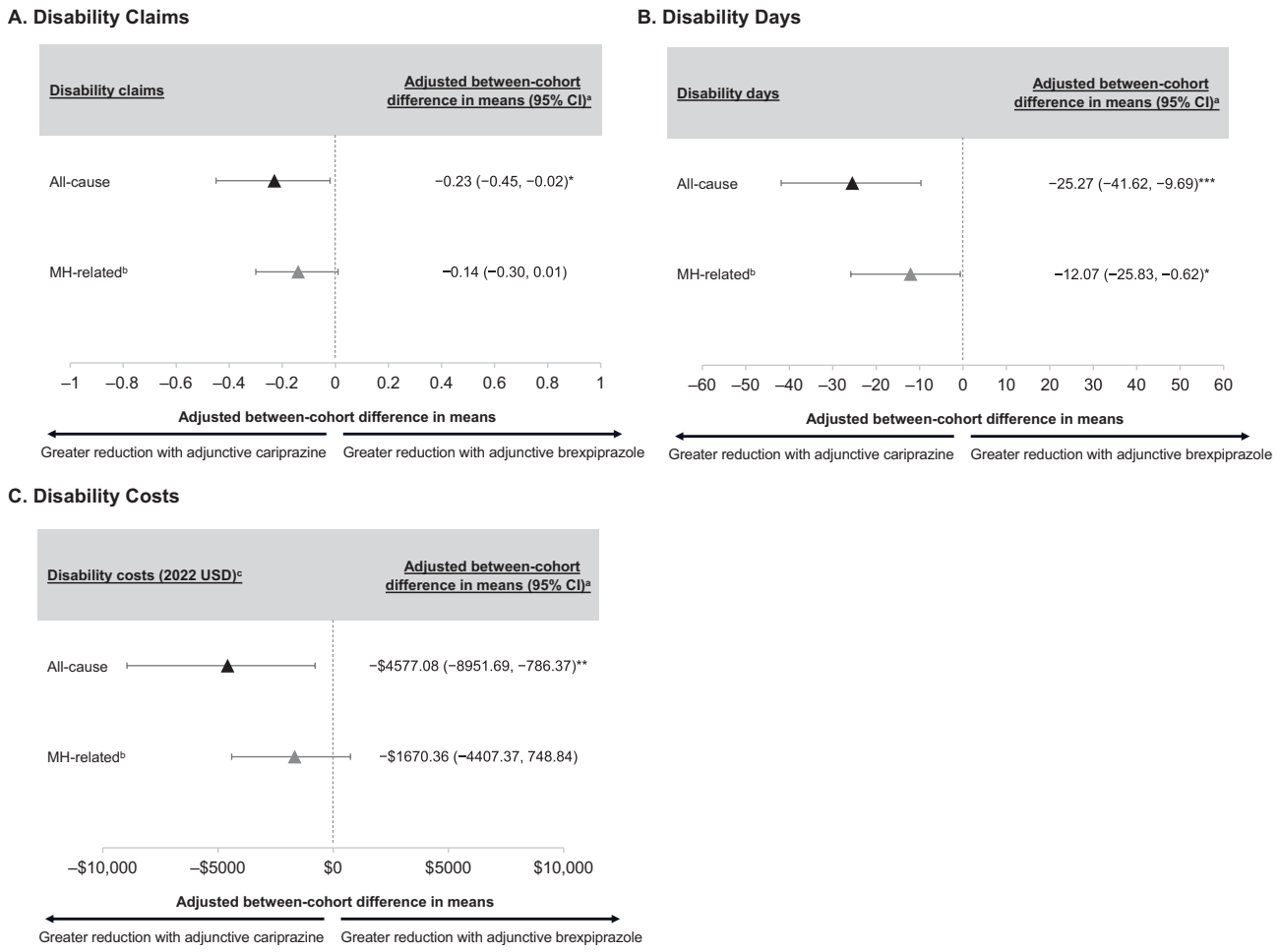

Figure 2 Adjusted Mean Between-Cohort Difference in Disability Outcomes[a] With Adjunctive Cariprazine vs Adjunctive Brexpiprazole (**A**) Disability Claims (**B**) Disability Days (**C**) Disability Costs.

Notes: **P*<0.05, ***P*<0.01, ****P*<0.001 vs adjunctive brexpiprazole.[a]The difference-in-difference analysis evaluated the pre-post change in the outcome among patients treated with adjunctive cariprazine with the pre-post change in outcome among patients treated with the comparator AA (adjunctive brexpiprazole). Baseline patient characteristics that remained imbalanced after IPTW were included as covariates in the regression model. The estimate represents the absolute change in rates or mean costs PPY owing to being part of the cariprazine cohort.[b]MH-related disability outcomes were defined as claims with a primary or secondary MH diagnosis code.[c]Disability costs were defined as the sum of short- and long-term disability costs and inflated to 2022 USD using US hourly compensation price index. If disability payments were zero or unavailable for a patient, they were estimated based on the number of disability days, median hourly wage of $22.26, and earnings replacement rate of 60%.

Abbreviations: AA, atypical antipsychotic; IPTW, inverse probability of treatment weighting; MH, mental health; PPY, per patient-year; USD, US dollar.

44 years old, 63%–64% of patients were female, 73%-75% of patients had a comorbid anxiety disorder, and the average length of follow-up was approximately 4 months (Table 3; Supplementary Tables 5 and 6).

All-cause baseline disability claims were 0.51 PPY and 0.51 PPY for adjunctive cariprazine and adjunctive aripiprazole, respectively, and disability claims during follow-up were 0.42 PPY and 0.37 PPY, respectively (Table 4). Additionally, MH-related baseline disability claims were 0.26 PPY and 0.25 PPY for cariprazine and aripiprazole, respectively, and MH-related follow-up disability claims were 0.17 PPY and 0.18 PPY, respectively. The reductions in all-cause and MH-related disability claims were not significantly greater for adjunctive cariprazine relative to adjunctive aripiprazole (adjusted between-cohort difference in means [95% CI], all-cause: −0.11 [−0.30, 0.11], *P*=0.321; MH-related : −0.08 [−0.21, 0.07], *P*=0.2855; Figure 3A). Baseline all-cause disability days were 33.61 PPY for adjunctive cariprazine and 34.15 PPY for adjunctive aripiprazole, while follow-up disability days were 20.29 PPY and 25.15 PPY, respectively. Further, MH-related baseline and follow-up disability days were 20.72 PPY and 11.91 PPY for adjunctive cariprazine, respectively, and 20.13 PPY and 12.36 PPY for adjunctive aripiprazole, respectively. Similar to

Table 3 Baseline Demographics and Clinical Characteristics: Adjunctive Cariprazine Vs Adjunctive Aripiprazole

Characteristic	Weighted Cohorts[a]		Std diff[b] (%)
	Adjunctive Cariprazine (n=174)	Adjunctive Aripiprazole (n=2931)	
Age, mean (SD), y	44.3 (10.1)	44.1 (10.5)	2.4
Female, n (%)	111 (63.8)	1840 (62.8)	2.2
Geographic region, n (%)			
Midwest	53 (30.6)	804 (27.4)	7.0
Northeast	9 (4.9)	320 (10.9)	22.2
South	82 (47.1)	1231 (42.0)	10.4
West	24 (14.1)	535 (18.3)	11.4
Unknown	6 (3.3)	41 (1.4)	12.3
Physician specialty at index,[c] n (%)			
Primary care	77 (44.3)	1073 (36.6)	15.6
MH specialist	80 (46.2)	1624 (55.4)	18.5
Other provider type	14 (7.9)	205 (7.0)	3.4
Missing	3 (1.6)	29 (1.0)	5.9
Quan-CCI,[d] mean (SD)	0.44 (1.01)	0.46 (0.97)	1.4
Top baseline DSM-5 comorbidities,[d] n (%)			
Anxiety disorders	127 (72.8)	2188 (74.6)	4.3
Sleep-wake disorders	65 (37.1)	969 (33.1)	8.5
Trauma- and stressor-related disorders	42 (24.1)	737 (25.1)	2.4
Substance-related and addictive disorders	41 (23.3)	593 (20.2)	7.5
Bipolar and related disorders	25 (14.2)	310 (10.6)	11.1
Baseline MH medication use,[d,e] n (%)			
Adjunctive AAs (excluding index AA)	35 (20.4)	417 (14.2)	16.2
Mood stabilizers	2 (1.2)	37 (1.3)	0.2
Thyroid hormone	2 (1.1)	37 (1.3)	1.9
Other adjunctive and supportive therapies	24 (14.0)	443 (15.1)	3.2

Notes: [a]Cohorts were weighted using IPTW based on propensity scores. Variables used in the propensity score calculation included age at index date, sex, geographic region, year of index date, physician specialty around index, baseline Quan-CCI score, baseline MDD severity, baseline MH-related therapy use, baseline other supportive therapy use, other MH-related therapy used during baseline, baseline all-cause healthcare resource utilization (hospitalizations, ED visits, outpatient visits), baseline all-cause medical costs, and DSM-5 and Elixhauser comorbidities with std diffs >10% and a prevalence in cariprazine cohort ≥5%. The weight was trimmed at 99% of the distribution. Counts are rounded to the nearest integer, while percentages are calculated from continuous weighted values.[b]For continuous variables, the std diff is calculated by dividing the absolute difference in means of the control and the case by the pooled SD of both groups. The pooled SD is the square root of the average of the squared SDs. For dichotomous variables, the std diff is calculated using the following equation where P is the respective proportion of participants in each group: $|(Pcase–Pcontrol)| / \sqrt{[(Pcase(1–Pcase)+Pcontrol(1–Pcontrol))/2]}$.[c]Evaluated during the 45 days pre-index and 15 days post-index. MH specialists included psychiatrist, psychologist, psychiatric nurse, and child psychiatrist. Primary care physicians included family practice, internal medicine, pediatrician, hospitalist, multispecialty physician group, medical doctor, nursing services, and nurse practitioner. For patients with claims for both primary care physicians and MH specialists, physician type was classified as specialist. Patients with claims with a nonmissing provider type that did not belong to any of the other categories were classified as other provider type (not elsewhere classified).[d]Evaluated during the 12-month baseline period, excluding the index date.[e]Per study design, all patients were prescribed ≥1 ADT during the baseline period.

Abbreviations: AA, atypical antipsychotic; ADT, antidepressant therapy; CCI, Charlson Comorbidity Index; DSM-5, *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition*; ED, emergency department; IPTW, inverse probability of treatment weighting; MDD, major depressive disorder; MH, mental health; std diff, standardized difference.

disability claims, the reductions in disability days were not significantly greater for adjunctive cariprazine compared with adjunctive aripiprazole (all-cause: −10.65 [−24.26, 0.75], *P*=0.072; −7.22 [−18.13, 2.40], *P*=0.144; Figure 3B).

Among adjunctive cariprazine users, all-cause disability costs were $7058.61 PPY during the baseline period and $2696.84 PPY during the follow-up period; among adjunctive aripiprazole users, baseline and follow-up costs were $6260.88 PPY and $4535.90 PPY, respectively. The reduction in all-cause disability costs PPY was statistically significantly greater with adjunctive cariprazine compared with adjunctive aripiprazole (adjusted between-cohort difference in means [95% CI]: −$3275.91 [−6431.07, −724.48], *P*=0.004; Figure 3C). Similarly, MH-related disability costs

Table 4 Frequency and Rates of Short- and Long-Term Disability Outcomes: Adjunctive Cariprazine Vs Adjunctive Aripiprazole

Short- and Long-Term Disability Outcomes	Frequency		Baseline Rate (PPY)		Follow-Up Rate (PPY)	
	Adjunctive Cariprazine	Adjunctive Aripiprazole	Adjunctive Cariprazine	Adjunctive Aripiprazole	Adjunctive Cariprazine	Adjunctive Aripiprazole
Number of eligible patients	174	2931	–	–	–	–
Follow-up period[a], mean ± SD, y	0.33±0.22	0.37±0.22	–	–	–	–
Disability claims						
All-cause	26	390	0.51	0.51	0.42	0.37
MH-related[b]	10	176	0.26	0.25	0.17	0.18
Disability days						
All-cause	1218	25,312	33.61	34.15	20.29	25.15
MH-related[b]	580	12,499	20.72	20.13	11.91	12.36
Disability costs (2022 USD)[c]						
All-cause	–	–	$7058.61	$6260.88	$2696.84	$4535.90
MH-related[b]	–	–	$4009.08	$3728.92	$1341.92	$2377.54

Notes: [a]The follow-up period spans from the index date to the earliest of 1 year post-index, end of HPM or health insurance eligibility, diagnosis of schizophrenia or schizoaffective disorder, claim for a non-index AA, discontinuation of AA or ADT, or end of data availability.[b]MH-related disability was defined as events with a primary or secondary MH diagnosis code.[c]Disability costs were defined as the sum of short- and long-term disability costs. If disability payments were zero or unavailable for a patient, they were estimated based on the number of disability days, median daily earnings rate (estimated using a median hourly wage of $22.26 based on the May 2022 National Occupational Employment and Wage Estimates for all occupations from the US Department of Labor Bureau of Labor Statistics), and earnings replacement rate of 60%. Costs were adjusted to 2022 USD using the US hourly compensation price index. The imputation of missing or zero costs was performed separately for MH-related and non–MH-related costs. Where either component was imputed, all-cause costs were calculated as the sum of MH-related and non–MH-related costs, whether imputed or available.

Abbreviations: AA, atypical antipsychotic; ADT, antidepressant therapy; HPM, Health and Productivity Management Database; MH, mental health; PPY, per patient-year; USD, US dollar.

during baseline and follow-up were $4009.08 PPY and $1341.92 PPY for adjunctive cariprazine users, respectively, and $3728.92 PPY and $2377.54 PPY for adjunctive aripiprazole users, respectively. The reduction was statistically significantly greater with adjunctive cariprazine vs adjunctive aripiprazole (−$2196.36 [−4269.51, −227.68], P=0.028).

Discussion

Despite MDD being a leading cause of disability worldwide,[1] little research has been conducted analyzing the effects of medications on real-world disability outcomes. Although previous clinical trials have evaluated disability outcomes in patients with MDD treated with adjunctive AAs using patient reported outcomes,[31,32] this claims-based analysis used real-world medical and disability claims to evaluate the changes in disability outcomes before and after treatment with adjunctive cariprazine vs adjunctive brexpiprazole or adjunctive cariprazine vs adjunctive aripiprazole. Results demonstrated that adjunctive cariprazine was associated with significantly lower rates of disability claims and days relative to adjunctive brexpiprazole, while rates were similar for adjunctive cariprazine vs adjunctive aripiprazole. Further, adjunctive cariprazine was associated with significantly greater reductions in all-cause disability costs vs adjunctive brexpiprazole and both all-cause and MH-related disability costs vs adjunctive aripiprazole. These results underscore the extent to which adjunctive AA choice may have real-world implications on disability outcomes in patients with MDD.

The results of our analysis differed when comparing adjunctive cariprazine to adjunctive brexpiprazole and adjunctive cariprazine to adjunctive aripiprazole. In the cariprazine vs brexpiprazole analysis, greater reductions in favor of cariprazine were observed for all outcomes, with statistically significantly greater reductions in all-cause disability claims, days, and costs as well as statistically significantly greater reductions in MH-related disability days. In the cariprazine vs aripiprazole analysis, all-cause and MH-related costs showed a statistically significantly greater reduction in favor of cariprazine vs aripiprazole, while only numerically greater reductions in favor of cariprazine were observed for all other outcomes. The reason for the lack of statistical significance on all-cause and MH-related disability claims and days may be, in part, owing to the smaller cariprazine cohort sample size in the cariprazine vs aripiprazole comparison. The relatively small sample size paired with the rarity of the disability events may compound to generate estimates that do not reach statistical significance at the 0.05 threshold.

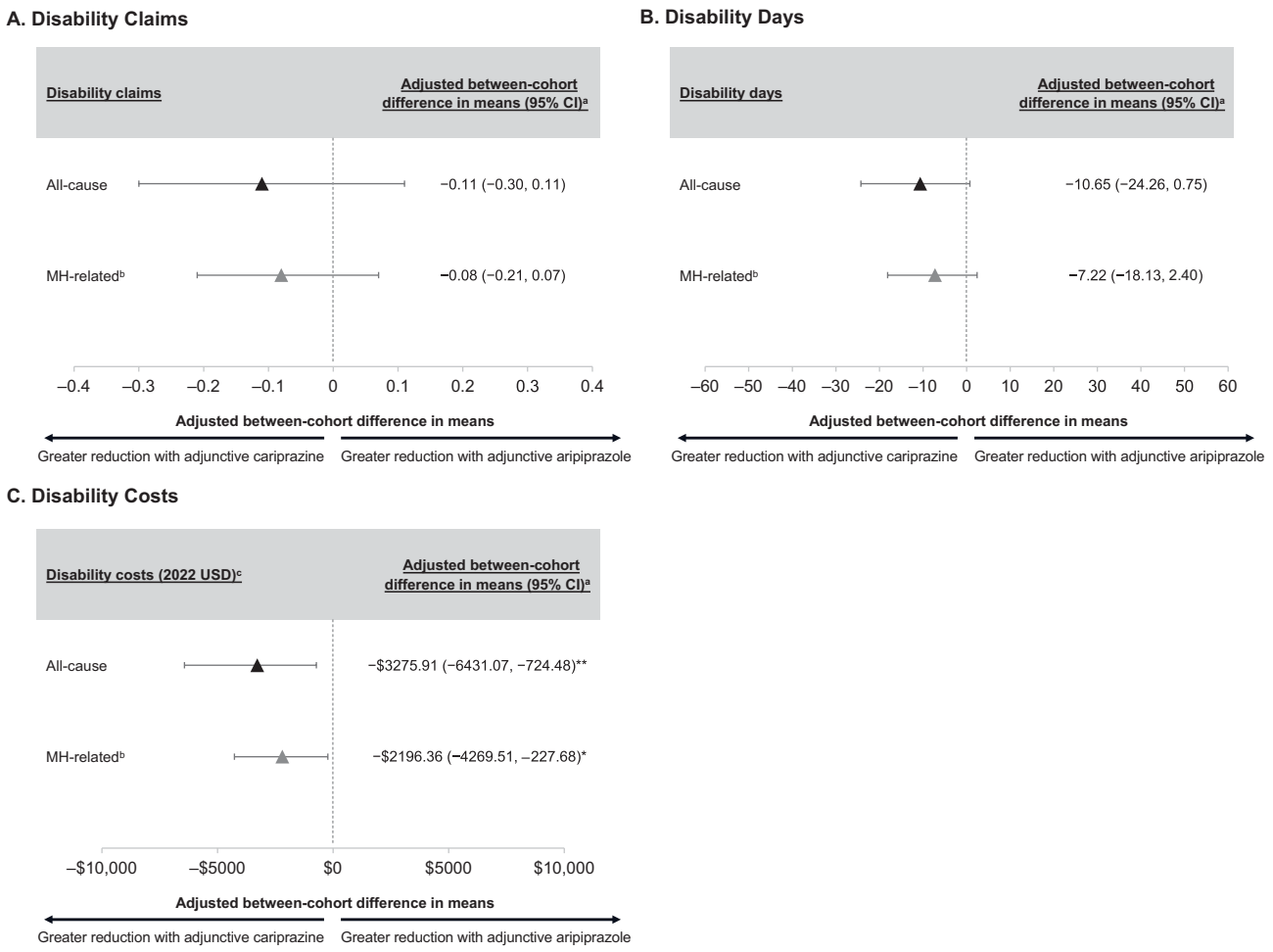

Figure 3 Adjusted Mean Between-Cohort Difference in Disability Outcomes[a] With Adjunctive Cariprazine vs Adjunctive Aripiprazole (**A**) Disability Claims (**B**) Disability Days (**C**) Disability Costs.

Notes: *$P<0.05$, **$P<0.01$ vs adjunctive aripiprazole.[a]The difference-in-difference analysis evaluated the pre-post change in the outcome among patients treated with adjunctive cariprazine with the pre-post change in outcome among patients treated with the comparator AA (adjunctive aripiprazole). Baseline patient characteristics that remained imbalanced after IPTW were included as covariates in the regression model. The estimate represents the absolute change in rates or mean costs PPY owing to being part of the cariprazine cohort.[b]MH-related disability outcomes were defined as claims with a primary or secondary MH diagnosis code.[c]Disability costs were defined as the sum of short- and long-term disability costs and inflated to 2022 USD using US hourly compensation price index. If disability payments were zero or unavailable for a patient, they were estimated based on the number of disability days, median hourly wage of $22.26, and earnings replacement rate of 60%.

Abbreviations: AA, atypical antipsychotic; IPTW, inverse probability of treatment weighting; MH, mental health; PPY, per patient-year; USD, US dollar.

The results of the present analysis also showed that disability claims, days, and costs were descriptively lower after treatment with adjunctive cariprazine compared with before treatment in patients with MDD. These results are consistent with a previous claims-based study, which compared disability outcomes during cariprazine treatment with the 12 months prior to cariprazine treatment in patients with MDD, bipolar I disorder, or schizophrenia.[33] The previous analysis found that patients treated with cariprazine had statistically significantly lower rates of all-cause and MH-related disability events and days during vs before cariprazine use. Disability-related costs were also significantly lower during cariprazine use than before the initiation of cariprazine. The present analysis supports previous findings and adds important context regarding how adjunctive cariprazine compares with other adjunctive AAs in reducing real-world disability outcomes and costs. Therefore, these results may be useful to clinicians, employers, payers, and other stakeholders when evaluating the choice of initial adjunctive AA treatment for patients with MDD.

Decreased rates of disability outcomes are important from a patient, provider, and societal prospective. From the patients' perspective, being unable to work due to disability can result in not only financial strain due to lost income but also negatively impact their emotional well-being and may increase stress and further exacerbate symptoms.[37]

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Conversely, steady employment has been shown to enhance self-esteem, improve quality of life, and reduce mental health service use.[38] As mental health services emphasize a holistic approach rather than just the treatment of symptoms, treatments that can help to reduce disability outcomes are also valuable from a provider's perspective.[39] Further, because poor functioning is closely associated with disability,[40] decreased disability claims and a decreased number of days on disability can be proxy indicators of improvement in a patient's functional recovery. Therefore, treatments such as cariprazine, which reduce the disability burden for patients and the accompanying economic burden, are valuable from multiple perspectives.

Disability associated with MDD is complex and multifactorial.[41,42] One major contributor is impairment in function, which often lags behind symptomatic recovery.[43] Although the reasoning for the improvements in disability outcomes observed in this study is unknown and the timeframe was limited, the observed disability improvements may be related to cariprazine's previously demonstrated efficacy on functional outcomes.[44–46] For example, in a post hoc analysis of a Phase 3 clinical trial, patients with MDD who received adjunctive cariprazine 1.5 mg/d or 3 mg/d had significant improvements in the 12-item Short-Form version 2 Health Survey domains of social functioning and role limitations owing to emotional problems relative to patients receiving adjunctive placebo.[46] Anhedonia, or the loss of interest or pleasure, is negatively correlated with function and may also play a role in the high rates of disability among patients with MDD.[47] In another post hoc analysis of a phase 3 clinical trial evaluating cariprazine for the treatment of MDD, adjunctive cariprazine was associated with improvement in symptoms of depression and anhedonia in patients with moderate to severe anhedonia at baseline.[48] Anxiety is also associated with disability and is highly comorbid with MDD,[30] which is supported by the current study where >70% of patients in both the cariprazine vs brexpiprazole and cariprazine vs aripiprazole analyses had comorbid anxiety. Cariprazine has previously been shown to decrease anxiety symptoms, with a post hoc analysis of clinical trial data demonstrating that adjunctive cariprazine for the treatment of MDD reduced anxiety symptoms as measured by mean reductions in Hamilton Rating Scale for Depression Anxiety/Somatization scores and Hamilton Anxiety Rating Scale total scores relative to placebo.[49] Although further studies are needed to confirm, the positive effects of cariprazine on a wide range of clinical symptoms may have contributed to the descriptively lower rates of disability outcomes and costs observed in this analysis. The efficacy cariprazine has demonstrated across multiple indications, coupled with the decreased disability burden observed in this real-world study, may be important considerations for prescribers when making clinical treatment decisions.

Although the underlying factors resulting in the differences in disability outcomes between cariprazine, brexpiprazole, and aripiprazole are unclear, the D_3-preferring pharmacology of cariprazine may play a role given the broad efficacy of cariprazine across depressive and other associated symptoms. While cariprazine, brexpiprazole, and aripiprazole are all dopamine partial agonists, the receptor binding profiles of these compounds differ. Unlike aripiprazole and brexpiprazole, which have a higher affinity for dopamine D_2 receptors than D_3 receptors, cariprazine has a greater affinity for D_3 over D_2.[22,24,50] D_3 receptors are expressed in areas of the brain thought to be involved in the modulation of reward, mood and motivation.[51] In preclinical rodent models, cariprazine was associated with anti-anhedonic and pro-cognitive effects, which were found to be mediated through the D_3 receptor.[52–55] These findings are further supported by clinical data, including the previously-mentioned analyses demonstrating effects of cariprazine on anxiety and anhedonia symptoms as well as other analyses showing cariprazine was associated with significant effects on cognitive symptoms in patients with bipolar I mania, bipolar I depression, and schizophrenia.[56] For example, a post hoc analysis evaluating cariprazine and aripiprazole vs placebo in patients with schizophrenia found that cariprazine 3 mg/d was associated with significantly greater improvements vs placebo in cognitive outcomes measuring focused attention and sustained attention, while aripiprazole was not.[56] However, the precise underlying factors resulting in differences in disability outcomes between these medications is unknown, and future research into the relationship between symptomatic improvement and improved disability outcomes is warranted.

Limitations

By using data from claims databases, this analysis was able to capture real-world outcomes of patients prescribed different adjunctive AAs; however, the results of this study are subject to limitations that are inherent to claims-based analyses. For example, claims data are vulnerable to omissions and coding errors, although it is not expected that this

would affect one cohort more than another. Further, because Merative MarketScan is a commercial database and because disability claims were obtained from employers, results may have limited generalizability to those in the US population with no insurance coverage, with other types of insurance such as Medicaid or Medicare, or who are unemployed. It should also be noted that a pharmacy claim for a dispensed medication does not necessarily indicate that the medication was taken as prescribed, and medications not recorded in the claims data (ie, over-the-counter medications, drug samples, or medications received during an inpatient stay) were not captured in the analysis. Additionally, both the Merative MarketScan and HPM databases may undercount productivity loss because unreported absenteeism and presenteeism are not recorded by the employer and therefore are not included in the database; however, it is expected that this limitation would equally affect both cohorts. The HPM database also does not include specific causes of disability, though it includes diagnosis codes associated with the disability event. Additionally, although a doubly robust approach was used to account for potential between-cohort differences, the possibility of residual confounding remains. The results were also not adjusted for multiple comparisons, although correcting for multiple comparisons is a subject of debate and may reduce power and increase type II errors, contributing to publication bias.[57,58] Moreover, we attempted to minimize bias by being intentionally inclusive in our covariate selection for the IPTW, but we acknowledge that residual confounding is always possible due to variables that are not available in claims data. It should also be noted that nonadherence is common in patients with MDD[59] and difficult to account for in claims-based analyses; however, follow-up ended once patients discontinued their medication. Another limitation is the short follow-up periods for the patient cohorts in this dataset, which limit the results from being applied to long-term outcomes. Further, inherent to retrospective, observational studies, causality cannot be determined from these data; however, these types of studies are commonly used to evaluate disability outcomes in the real-world.[60–62] Last, as cariprazine was not approved for the adjunctive use of MDD until December 2022, cariprazine was used off-label for the majority of the analysis, which may have resulted in the smaller samples sizes.

Conclusion

Among patients with MDD, adjunctive cariprazine was associated with significantly lower rates of disability claims and days compared with adjunctive brexpiprazole. Adjunctive cariprazine was also associated with significantly greater reductions in all-cause disability costs relative to adjunctive brexpiprazole and significantly greater reductions in all-cause and MH-related costs relative to adjunctive aripiprazole. Overall, these real-world outcomes highlight the importance of adjunctive AA choice in mitigating the burden of disability and demonstrate that adjunctive cariprazine may be a useful treatment option in managing the real-world burden of disability in patients with MDD.

Abbreviations

AA, atypical antipsychotic; ADT, antidepressant therapy; CCI, Charlson Comorbidity Index; ED, emergency department; FDA, US Food and Drug Administration; HPM, Health and Productivity Management; IPTW, inverse probability of treatment weighting; MDD, major depressive disorder; MH, mental health; PPY, per patient-year; Std diff, standardized difference; USD, US dollars.

Data Sharing Statement

Data are not available owing to commercial restrictions.

Ethical Approval and Informed Consent

This study was exempt from ethics committee approval and institutional review because it is a retrospective analysis that used anonymized and de-identified data certified as fully compliant with US patient confidentiality requirements set forth in the Health Insurance Portability and Accountability Act of 1996. Allergan (prior to its acquisition by AbbVie) obtained permission to access and use the Merative MarketScan and Health and Productivity Management data used in the analysis through licensing agreements.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

P.S. Masand has served as a consultant for Abbvie, Intra-Cellular Therapies, Karuna Therapeutics, Neumora Therapeutics, and Neurocrine Biosciences; has served on speaker's bureaus for AbbVie, BMS, Neurocrine Biosciences, and Vanda Pharmaceuticals; and has stock ownership in Relmada Therapeutics. M. Parikh, J. Ta, F. Haile, and N. Nabulsi are employees of AbbVie and may hold stock. S.W. Wade is a partner in Wade Outcomes Research and Consulting and a consultant for AbbVie. S. Ripley, E. Zanardo, C. Spencer, and F. Laliberté are employees of Analysis Group, which was funded by AbbVie to conduct the analyses. The authors report no other conflicts of interest in this work.

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