

SUPPLEMENTARY MATERIAL

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

Prakash S. Masand,¹ Mousam Parikh,² Jamie T. Ta,² Sally W. Wade,³ Filmon Haile,² Susannah Ripley,⁴ Enrico Zanardo,⁵ Colleen S. Spencer,⁴ François Laliberté,⁴ Nadia Nabulsi²

1. Duke-NUS, Singapore
2. AbbVie, North Chicago, IL, USA
3. Wade Outcomes Research and Consulting, Salt Lake City, UT, USA
4. Groupe d'analyse, Ltée, Montréal, QC, Canada
5. Analysis Group, Inc., Denver, CO, USA
6. Duke-NUS, Singapore
7. AbbVie, North Chicago, IL, USA
8. Wade Outcomes Research and Consulting, Salt Lake City, UT, USA
9. Groupe d'analyse, Ltée, Montréal, QC, Canada
10. Analysis Group, Inc., Denver, CO, USA

Supplementary Table 1. Atypical Antipsychotics and Antidepressant Therapies

Class	Description	GPI code
Atypical antipsychotic	Aripiprazole	59250015
Atypical antipsychotic	Brexpiprazole	59250020
Atypical antipsychotic	Cariprazine	59400018
NDRI	Bupropion	58300040, 62100002
SSRI	Citalopram	58160020
SSRI	Escitalopram	58160034, 5899850530B130
SSRI	Fluoxetine	58160040, 62206040
SSRI	Paroxetine	58160060, 62226060
SSRI	Sertraline	58160070
SSRI	Vortioxetine	58120093
SNRI	Desvenlafaxine	58180020
SNRI	Duloxetine	58180025
SNRI	Levomilnacipran	58180050

SNRI	Venlafaxine	58180090
TCAs and tetracyclic antidepressants	Amitriptyline	58200010
TCAs and tetracyclic antidepressants	Amitriptyline/chlordiazepoxide	62992002
TCAs and tetracyclic antidepressants	Amoxapine	58200020
TCAs and tetracyclic antidepressants	Clomipramine	58200025
TCAs and tetracyclic antidepressants	Desipramine	58200030
TCAs and tetracyclic antidepressants	Doxepin	58200040, 60400030
TCAs and tetracyclic antidepressants	Imipramine	58200050
TCAs and tetracyclic antidepressants	Maprotiline	58300010
TCAs and tetracyclic antidepressants	Nortriptyline	58200060
TCAs and tetracyclic antidepressants	Protriptyline	58200070
TCAs and tetracyclic antidepressants	Trimipramine	58200080
MAOI	Isocarboxazid	58100010
MAOI	Phenelzine	58100020
MAOI	Selegiline	58100027
MAOI	Tranylcypromine	58100030
Serotonin modulators	Nefazodone	58120050
Serotonin modulators	Trazodone	58120080
Serotonin modulators	Vilazodone	58120088
Other	Esketamine	58110020
Other	Fluvoxamine	58160045

Other	Mirtazapine	58030050
-------	-------------	----------

GPI, generic product identifier; MAOI, monoamine oxidase inhibitor; NDRI, norepinephrine-dopamine reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant.

Supplementary Table 2. List of ICD-10-CM Codes for Major Depressive Disorder

Diagnosis Code	Description
<i>F32</i>	<i>Major depressive disorder, single episode</i>
F32.0	Major depressive disorder, single episode, mild
F32.1	Major depressive disorder, single episode, moderate
F32.2	Major depressive disorder, single episode, severe without psychotic features
F32.3	Major depressive disorder, single episode, severe with psychotic features
F32.4	Major depressive disorder, single episode, in partial remission
F32.5	Major depressive disorder, single episode, in full remission
F32.9	Major depressive disorder, single episode, unspecified
<i>F33</i>	<i>Major depressive disorder, recurrent</i>
F33.0	Major depressive disorder, recurrent, mild
F33.1	Major depressive disorder, recurrent, moderate
F33.2	Major depressive disorder, recurrent severe without psychotic features
F33.3	Major depressive disorder, recurrent, severe with psychotic symptoms
F33.4	Major depressive disorder, recurrent, in remission
F33.40	Major depressive disorder, recurrent, in remission, unspecified
F33.41	Major depressive disorder, recurrent, in partial remission
F33.42	Major depressive disorder, recurrent, in full remission
F33.9	Major depressive disorder, recurrent, unspecified

ICD-10-CM, *International Classification of Diseases, 10th Revision, Clinical Modification*.

Supplementary Table 3. Baseline Demographics and Clinical Characteristics of Weighted and Unweighted Cohorts: Adjunctive Cariprazine vs Adjunctive Brexpiprazole

Characteristic	Unweighted cohorts			Weighted cohorts ^a		
	Adjunctive cariprazine (n=224)	Adjunctive brexpiprazole (n=643)	Std diff ^b (%)	Adjunctive cariprazine (n=224)	Adjunctive brexpiprazole (n=643)	Std diff ^b (%)
Length of follow-up period, mean (SD), mo	3.9 (2.6)	4.4 (2.6)	19.8	4.1 (2.6)	4.4 (2.6)	10.2
Demographics						
Age, mean (SD), y	44.0 (9.8)	46.3 (9.6)	23.0	45.4 (9.5)	45.7 (9.6)	3.1
Female, n (%)	140 (62.5)	396 (61.6)	1.9	143 (63.7)	398 (61.9)	3.8
Year of index date, n (%)						
2017	15 (6.7)	107 (16.6)	31.4	26 (11.6)	92 (14.4)	8.3
2018	21 (9.4)	143 (22.2)	35.8	38 (17.2)	123 (19.1)	5.1
2019	43 (19.2)	110 (17.1)	5.4	36 (16.1)	110 (17.2)	2.9
2020	50 (22.3)	81 (12.6)	25.8	37 (16.5)	97 (15.1)	4.1
2021	44 (19.6)	94 (14.6)	13.4	41 (18.5)	104 (16.1)	6.2
2022	51 (22.8)	108 (16.8)	15.0	45 (20.2)	117 (18.1)	5.2
Geographic region, n (%)						
South	103 (46.0)	316 (49.1)	6.3	106 (47.3)	313 (48.6)	2.5
Midwest	76 (33.9)	159 (24.7)	20.3	68 (30.3)	176 (27.4)	6.5
West	26 (11.6)	90 (14.0)	7.2	26 (11.4)	83 (12.9)	4.6
Northeast	13 (5.8)	63 (9.8)	14.9	17 (7.5)	56 (8.7)	4.5
Unknown	6 (2.7)	15 (2.3)	2.2	8 (3.4)	15 (2.4)	6.4
Physician specialty at index,^c n (%)						
Primary care	113 (50.4)	191 (29.7)	43.3	81 (36.4)	227 (35.2)	2.4
MH specialist	91 (40.6)	406 (63.1)	46.3	125 (55.7)	368 (57.2)	3.1
Other provider type	18 (8.0)	37 (5.8)	9.0	16 (7.4)	40 (6.2)	4.5
Missing	2 (0.9)	9 (1.4)	4.8	1 (0.6)	9 (1.4)	7.5
Quan-CCI,^d mean (SD)	0.38 (0.90)	0.53 (1.04)	14.8	0.54 (1.21)	0.49 (1.00)	4.3
Baseline MDD severity,^d n (%)						
Severe	57 (25.4)	199 (30.9)	12.3	66 (29.7)	193 (30.1)	0.9
Moderate	89 (39.7)	263 (40.9)	2.4	91 (40.5)	262 (40.7)	0.4
Mild	12 (5.4)	38 (5.9)	2.4	12 (5.3)	36 (5.6)	1.5
Remission	7 (3.1)	23 (3.6)	2.5	9 (4.0)	22 (3.4)	2.9
Unspecified	59 (26.3)	120 (18.7)	18.5	46 (20.6)	129 (20.1)	1.0
Baseline MH medication use,^{d,e} n (%)						
Adjunctive AAs (excluding index AA)	97 (43.3)	273 (42.5)	1.7	99 (44.1)	274 (42.7)	2.8
Mood stabilizer	9 (4.0)	6 (0.9)	20.0	5 (2.4)	6 (0.9)	11.6
Thyroid hormone	2 (0.9)	9 (1.4)	4.8	2 (0.8)	8 (1.2)	4.9
Other adjunctive and supportive therapies	43 (19.2)	108 (16.8)	6.3	35 (15.8)	104 (16.2)	1.2
Other baseline supportive therapy use,^d n (%)						
Benzodiazepines	104 (46.4)	354 (55.1)	17.3	119 (53.3)	344 (53.5)	0.4
Opioids	80 (35.7)	231 (35.9)	0.4	86 (38.6)	235 (36.5)	4.4
Stimulants	56 (25.0)	149 (23.2)	4.3	57 (25.4)	152 (23.7)	3.9
Treatments for sleep disturbances	32 (14.3)	126 (19.6)	14.2	47 (20.9)	122 (19.0)	4.6
Other	6 (2.7)	31 (4.8)	11.3	7 (3.3)	31 (4.8)	7.6
Other baseline MH-related therapy,^d n (%)						
Psychotherapy	129 (57.6)	467 (72.6)	32.0	152 (67.8)	445 (69.2)	3.0
Psychiatric diagnostic evaluation	96 (42.9)	327 (50.9)	16.1	101 (45.0)	313 (48.6)	7.2

TMS	3 (1.3)	22 (3.4)	13.7	5 (2.3)	20 (3.1)	4.5
Psychological and neuropsychological assessment and testing	2 (0.9)	13 (2.0)	9.4	3 (1.1)	12 (1.8)	5.7
ECT	1 (0.4)	2 (0.3)	2.2	1 (0.5)	3 (0.5)	0.1
Baseline healthcare resource utilization,^d mean (SD)						
<i>All-cause</i>						
Hospitalizations	0.25 (0.5)	0.19 (0.56)	11.2	0.21 (0.53)	0.22 (0.62)	1.2
ED visits	1.1 (1.9)	0.94 (1.79)	11.0	1.0 (1.7)	1.0 (2.0)	0.1
Outpatient visits	28.3 (24.8)	30.8 (20.7)	10.8	29.8 (24.1)	30.2 (21.0)	2.0
<i>MH-related^f</i>						
Hospitalizations	0.23 (0.56)	0.15 (0.51)	13.9	0.18 (0.49)	0.18 (0.55)	1.6
ED visits	0.33 (0.89)	0.25 (0.71)	9.4	0.26 (0.69)	0.27 (0.75)	1.0
Outpatient visits	18.0 (21.7)	18.2 (16.8)	1.1	19.0 (21.1)	17.9 (17.2)	5.5
Baseline healthcare costs,^{d,g} mean (SD), 2022 USD						
<i>All-cause</i>						
Total healthcare costs (medical + pharmacy)	\$45,685 (72,835)	\$48,161 (83,490)	3.2	\$46,805 (71,014)	\$49,359 (86,517)	3.2
Medical costs	\$41,115 (71,568)	\$42,173 (81,155)	1.4	\$41,973 (69,624)	\$43,564 (34,284)	2.1
Hospitalization costs	\$11,199 (31,118)	\$9,555 (34,620)	5.0	\$9,891 (29,583)	\$10,602 (36,395)	2.1
ED visit costs	\$10,089 (20,616)	\$9,810 (22,574)	1.3	\$9,848 (19,656)	\$10,377 (23,798)	2.4
Outpatient visits costs	\$19,826 (27,298)	\$22,808 (36,730)	9.2	\$22,234 (30,457)	\$22,586 (35,910)	1.1
Physician office visit costs	\$19,048 (26,185)	\$22,055 (35,914)	9.6	\$21,311 (29,543)	\$21,827 (35,070)	1.6
Home health care visit costs	\$3,333 (12,400)	\$3,694 (12,816)	2.9	\$3,999 (13,546)	\$3,498 (12,363)	3.9
Other outpatient visit costs	\$7,235 (16,352)	\$8,318 (21,238)	5.7	\$8,308 (17,312)	\$8,576 (21,659)	1.4
Pharmacy costs	\$4,570 (12,026)	\$5,988 (12,527)	11.6	\$4,832 (12,595)	\$5,795 (12,191)	7.8
<i>MH-related^f</i>						
Total healthcare costs (medical + pharmacy)	\$37,404 (66,265)	\$37,475 (74,272)	0.1	\$37,433 (63,658)	\$39,087 (78,037)	2.3
Medical costs	\$35,980 (66,097)	\$35,625 (74,110)	0.5	\$35,921 (63,465)	\$37,246 (77,786)	1.9
Hospitalization costs	\$10,448 (29,317)	\$9,003 (33,568)	4.6	\$9,128 (27,561)	\$10,014 (35,381)	2.8
ED visit costs	\$9,390 (19,783)	\$9,009 (21,509)	1.8	\$9,252 (18,900)	\$9,481 (22,482)	1.1
Outpatient visit costs	\$16,141 (22,962)	\$17,614 (27,840)	5.8	\$17,541 (24,574)	\$17,750 (28,045)	0.8
Physician office visit costs	\$15,972 (22,828)	\$17,467 (27,716)	5.9	\$17,286 (24,498)	\$17,599 (27,901)	1.2
Home health care visit costs	\$2,934 (10,222)	\$3,556 (12,519)	5.4	\$3,609 (11,830)	\$3,371 (12,085)	2.0
Other outpatient visit costs	\$7025 (16,136)	\$7,835 (20,353)	4.4	\$8,030 (17,029)	\$8,081 (20,763)	0.3
Pharmacy costs	\$1,424 (2,447)	\$1,849 (3,470)	14.2	\$1,512 (2,414)	\$1,842 (3,422)	11.1

^aCohorts 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 $\geq 5\%$. The weight was trimmed at 99% of the distribution. Counts are rounded to the nearest integer, while percentages are calculated from continuous weighted values.

^bFor 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: $|(\text{Pcase} - \text{Pcontrol})| / \sqrt{[(\text{Pcase}(1 - \text{Pcase}) + \text{Pcontrol}(1 - \text{Pcontrol})) / 2]}$.

^cEvaluated 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).

^dEvaluated during the 12-month baseline period, excluding the index date.

^ePer study design, all patients were prescribed ≥ 1 ADT during the baseline period.

^fMH-related HRU and costs were defined as visits with a primary or secondary MH diagnosis code.

^gCosts were inflated to 2022 USD using the US Medical Care consumer price index from the Bureau of Labor Statistics from the US Department of Labor.

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

Supplementary Table 4. Baseline Comorbidities^a of Weighted and Unweighted Cohorts: Adjunctive Cariprazine vs Adjunctive Brexpiprazole

Characteristic	Unweighted cohorts			Weighted cohorts ^c		
	Adjunctive cariprazine (n=224)	Adjunctive brexpiprazole (n=643)	Std diff ^b (%)	Adjunctive cariprazine (n=224)	Adjunctive brexpiprazole (n=643)	Std diff ^b (%)
DSM-5 comorbidities, n (%)						
Anxiety disorders	171 (76.3)	469 (72.9)	7.8	172 (76.9)	471 (73.3)	8.3
Sleep-wake disorders	89 (39.7)	229 (35.6)	8.5	92 (40.9)	221 (34.4)	13.3
Trauma- and stressor-related disorders	62 (27.7)	164 (25.5)	4.9	54 (24.3)	169 (26.2)	4.4
Bipolar and related disorders	60 (26.8)	68 (10.6)	42.5	36 (15.9)	93 (14.4)	4.2
Substance-related and addictive disorders	59 (26.3)	120 (18.7)	18.5	44 (19.7)	126 (19.5)	0.3
Other conditions that may require a focus of clinical attention	44 (19.6)	142 (22.1)	6.0	46 (20.6)	147 (22.9)	5.6
Breathing-related sleep disorder	42 (18.8)	137 (21.3)	6.4	43 (19.2)	131 (20.3)	3.0
Obsessive-compulsive and related disorders	13 (5.8)	37 (5.8)	0.2	14 (6.5)	39 (6.0)	1.9
Schizophrenia spectrum and other psychotic disorders	10 (4.5)	5 (0.8)	23.2	4 (1.6)	8 (1.2)	3.7
Feeding and eating disorders	9 (4.0)	19 (3.0)	5.8	7 (3.0)	20 (3.2)	0.9
Other mental disorders	7 (3.1)	22 (3.4)	1.7	4 (1.8)	22 (3.5)	10.2
Personality disorders	6 (2.7)	15 (2.3)	2.2	9 (4.2)	17 (2.7)	8.3
Parasomnia disorders	6 (2.7)	14 (2.2)	3.3	7 (3.0)	14 (2.1)	5.2
Neurocognitive disorders	3 (1.3)	15 (2.3)	7.4	1 (0.5)	17 (2.6)	16.9
Medication-induced movement disorders and other adverse effects of medication	3 (1.3)	6 (0.9)	3.8	2 (0.8)	6 (1.0)	1.5
Sexual dysfunctions	1 (0.4)	6 (0.9)	5.9	0 (0.2)	6 (0.9)	9.8
Somatic symptom and related disorders	0 (0.0)	5 (0.8)	12.5	0 (0.0)	5 (0.8)	12.4
Elixhauser comorbidities, n (%)						
Hypertension	88 (39.3)	243 (37.8)	3.1	85 (38.0)	239 (37.2)	1.7
Obesity	63 (28.1)	152 (23.6)	10.3	52 (23.4)	160 (24.9)	3.6
Diabetes	37 (16.5)	89 (13.8)	7.5	33 (14.8)	90 (14.1)	2.2
Drug abuse	33 (14.7)	47 (7.3)	23.9	27 (12.1)	50 (7.7)	14.6
Chronic pulmonary disease	32 (14.3)	97 (15.1)	2.3	33 (14.6)	96 (14.9)	0.9
Hypothyroidism	31 (13.8)	108 (16.8)	8.2	40 (17.8)	103 (16.0)	4.7
Alcohol abuse	26 (11.6)	66 (10.3)	4.3	17 (7.6)	69 (10.7)	10.6
Cardiac arrhythmias	22 (9.8)	61 (9.5)	1.1	18 (8.2)	66 (10.3)	7.2
Fluid and electrolyte disorders	17 (7.6)	36 (5.6)	8.0	17 (7.8)	36 (5.7)	8.4
Rheumatoid arthritis/collagen vascular disease	14 (6.3)	49 (7.6)	5.4	15 (6.5)	50 (7.7)	4.6
Psychoses	10 (4.5)	5 (0.8)	23.2	4 (1.6)	8 (1.2)	3.7

Deficiency anemias	10 (4.5)	45 (7.0)	10.9	7 (2.9)	44 (6.8)	18.1
Liver disease	9 (4.0)	38 (5.9)	8.7	6 (2.7)	34 (5.3)	13.1
Weight loss	7 (3.1)	21 (3.3)	0.8	7 (3.1)	18 (2.8)	1.4
Other neurological disorder	6 (2.7)	34 (5.3)	13.4	4 (1.8)	37 (5.7)	21.0
Coagulopathy	5 (2.2)	13 (2.0)	1.5	3 (1.4)	15 (2.3)	6.7
Valvular disease	4 (1.8)	24 (3.7)	11.9	3 (1.1)	24 (3.7)	16.9
Renal failure	4 (1.8)	8 (1.2)	4.4	8 (3.5)	7 (1.1)	15.8
Peripheral vascular disorders	3 (1.3)	12 (1.9)	4.2	2 (0.8)	12 (1.9)	9.3
Solid tumor without metastasis	3 (1.3)	20 (3.1)	12.0	8 (3.4)	18 (2.8)	3.6
Blood loss anemia	3 (1.3)	11 (1.7)	3.0	2 (0.8)	14 (2.1)	10.8
Congestive heart failure	2 (0.9)	10 (1.6)	6.0	2 (0.9)	9 (1.3)	4.4
HIV/AIDS	2 (0.9)	3 (0.5)	5.2	4 (1.8)	3 (0.4)	13.2
Metastatic cancer	1 (0.4)	3 (0.5)	0.3	4 (1.6)	3 (0.5)	11.1
Peptic ulcer disease	1 (0.4)	4 (0.6)	2.4	1 (0.3)	4 (0.6)	4.8
Pulmonary circulation disorder	0 (0.0)	3 (0.5)	9.7	0 (0.0)	3 (0.4)	9.5
Paralysis	0 (0.0)	3 (0.5)	9.7	0 (0.0)	4 (0.6)	11.2

^aEvaluated during the 12-month baseline period, excluding the index date.

^bFor 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: $|(\text{Pcase} - \text{Pcontrol})| / \sqrt{[(\text{Pcase}(1 - \text{Pcase}) + \text{Pcontrol}(1 - \text{Pcontrol})) / 2]}$.

^cCohorts 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 $\geq 5\%$. The weight was trimmed at 99% of the distribution. Counts are rounded to the nearest integer, while percentages are calculated from continuous weighted values.

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.

Supplementary Table 5. Baseline Demographics and Clinical Characteristics of Weighted and Unweighted Cohorts: Adjunctive Cariprazine vs Adjunctive Aripiprazole

Characteristic	Unweighted cohorts			Weighted cohorts ^a		
	Adjunctive cariprazine (n=174)	Adjunctive aripiprazole (n=2931)	Std diff ^b (%)	Adjunctive cariprazine (n=174)	Adjunctive aripiprazole (n=2931)	Std diff ^b (%)
Length of follow-up period, mean (SD), mo.	4.0 (2.6)	4.5 (2.7)	19.0	4.1 (2.7)	4.5 (2.7)	12.4
Demographics						
Age, mean (SD), y	43.9 (10.0)	44.1 (10.6)	1.4	44.3 (10.1)	44.1 (10.5)	2.4
Female, n (%)	103 (59.2)	1844 (62.9)	7.6	111 (63.8)	1840 (62.8)	2.2
Year of index date, n (%)						
2017	11 (6.3)	591 (20.2)	41.7	20 (11.3)	569 (19.4)	22.6
2018	18 (10.3)	532 (18.2)	22.5	23 (13.1)	519 (17.7)	12.6
2019	36 (20.7)	483 (16.5)	10.8	34 (19.5)	490 (16.7)	7.2
2020	39 (22.4)	455 (15.5)	17.6	36 (20.6)	467 (15.9)	12.4
2021	32 (18.4)	448 (15.3)	8.3	31 (17.7)	453 (15.4)	5.7
2022	38 (21.8)	422 (14.4)	19.4	31 (17.7)	434 (14.8)	8.1
Region, n (%)						
South	80 (46.0)	1221 (41.7)	8.7	82 (47.1)	1231 (42.0)	10.4
Midwest	61 (35.1)	790 (27.0)	17.6	53 (30.6)	804 (27.4)	7.0
West	21 (12.1)	546 (18.6)	18.3	24 (14.1)	535 (18.3)	11.4
Northeast	6 (3.4)	333 (11.4)	30.6	9 (4.9)	320 (10.9)	22.2
Unknown	6 (3.4)	41 (1.4)	13.4	6 (3.3)	41 (1.4)	12.3
Physician specialty at index, ^c n (%)						
Primary care	89 (51.1)	1050 (35.8)	31.3	77 (44.3)	1073 (36.6)	15.6
MH specialist	71 (40.8)	1649 (56.3)	31.3	80 (46.2)	1624 (55.4)	18.5
Other provider type	12 (6.9)	204 (7.0)	0.3	14 (7.9)	205 (7.0)	3.4
Missing	2 (1.1)	28 (1.0)	1.9	3 (1.6)	29 (1.0)	5.9
Quan-CCI, ^d mean (SD)	0.45 (0.98)	0.46 (0.97)	0.4	0.44 (1.01)	0.46 (0.97)	1.4
Baseline MDD severity, ^d n (%)						
Severe	44 (25.3)	858 (29.3)	9.0	45 (25.7)	851 (29.0)	7.4
Moderate	65 (37.4)	1091 (37.2)	0.3	63 (36.5)	1094 (37.3)	1.7
Mild	11 (6.3)	189 (6.4)	0.5	11 (6.1)	188 (6.4)	1.4
Remission	7 (4.0)	131 (4.5)	6.8	10 (5.6)	131 (4.5)	5.3
Unspecified	47 (27.0)	662 (22.6)	0.7	45 (26.1)	668 (22.8)	7.7
Baseline MH-related therapy use^{d,e} n (%)						
Adjunctive AAs (excluding index AA)	60 (34.5)	383 (13.1)	52.0	35 (20.4)	417 (14.2)	16.2
Mood stabilizer	7 (4.0)	33 (1.1)	18.4	2 (1.2)	37 (1.3)	0.2
Thyroid hormone	3 (1.7)	37 (1.3)	3.8	2 (1.1)	37 (1.3)	1.9
Other adjunctive therapies	28 (16.1)	441 (15.0)	2.9	24 (14.0)	443 (15.1)	3.2
Other baseline supportive therapy use, ^d n (%)						
Benzodiazepines	87 (50.0)	1384 (47.2)	5.6	87 (49.9)	1389 (47.4)	5.0
Opioids	64 (36.8)	1043 (35.6)	2.5	63 (36.5)	1048 (35.8)	1.5
Stimulants	43 (24.7)	430 (14.7)	25.5	38 (21.8)	445 (15.2)	17.1
Treatments for sleep disturbances	22 (12.6)	367 (12.5)	0.4	20 (11.4)	369 (12.6)	3.6
Other	5 (2.9)	69 (2.4)	3.3	7 (3.9)	71 (2.4)	8.3
Other baseline MH-related therapy, ^d n (%)						
Psychotherapy	99 (56.9)	1814 (61.9)	10.2	99 (56.7)	1806 (61.6)	9.9
Psychiatric diagnostic evaluation	79 (45.4)	1413 (48.2)	5.6	75 (43.3)	1406 (48.0)	9.5

TMS	2 (1.1)	20 (0.7)	4.9	1 (0.4)	20 (0.7)	4.2
Psychological and neuropsychological assessment and testing	1 (0.6)	46 (1.6)	9.7	1 (0.4)	46 (1.6)	12.1
ECT	1 (0.6)	12 (0.4)	2.4	2 (1.1)	12 (0.4)	8.2
Baseline healthcare resource utilization,^d mean (SD)						
<i>All-cause</i>						
Hospitalizations	0.25 (0.64)	0.26 (0.63)	1.4	0.25 (0.65)	0.26 (0.63)	1.6
ED visits	1.1 (1.9)	1.1 (1.9)	0.6	1.1 (1.9)	1.1 (1.9)	3.2
Outpatient visits	28.2 (24.8)	26.2 (21.1)	8.5	26.5 (25.8)	26.3 (21.4)	0.7
<i>MH-related^f</i>						
Hospitalizations	0.22 (0.60)	0.22 (0.57)	1.1	0.21 (0.59)	0.22 (0.57)	1.5
ED visits	0.30 (0.89)	0.32 (0.88)	2.7	0.26 (0.81)	0.32 (0.88)	7.4
Outpatient visits	17.5 (22.3)	14.3 (16.1)	16.6	16.9 (23.4)	14.3 (16.1)	13.0
Baseline healthcare costs,^{d,g} mean (SD), 2022 USD						
<i>All-cause</i>						
Total healthcare costs (medical + pharmacy)	\$49,387 (80,876)	\$58,702 (163,417)	7.2	\$51,059 (85,924)	\$58,210 (160,424)	5.6
Medical costs	\$43,672 (79,049)	\$53,635 (158,409)	8.0	\$46,665 (84,723)	\$53,099 (155,456)	5.1
Hospitalization costs	\$11,595 (32,790)	\$14,684 (63,870)	6.1	\$12,834 (36,008)	\$14,514 (62,796)	3.3
ED visit costs	\$11,192 (23,040)	\$12,840 (40,820)	5.0	\$11,956 (24,968)	\$12,753 (40,141)	2.4
Outpatient visits costs	\$20,885 (29,789)	\$26,111 (65,909)	10.2	\$21,875 (31,496)	\$25,832 (64,518)	7.8
Physician office visit costs	\$20,069 (28,493)	\$24,999 (63,207)	10.1	\$20,829 (29,719)	\$24,724 (61,859)	8.0
Home health care visit costs	\$4557 (15,387)	\$5488 (32,620)	3.6	\$4325 (16,464)	\$5467 (32,099)	4.5
Other outpatient visit costs	\$7433 (17,772)	\$9482 (36,467)	7.1	\$7315 (17,938)	\$9425 (35,712)	7.5
Pharmacy costs	\$5716 (13,658)	\$5066 (30,683)	2.7	\$4394 (10,773)	\$5110 (30,465)	3.1
<i>MH-related^f</i>						
Total healthcare costs (medical + pharmacy)	\$39,999 (71,661)	\$45,958 (135,436)	5.5	\$41,679 (76,795)	\$45,611 (132,976)	3.6
Medical costs	\$37,725 (71,623)	\$45,123 (135,377)	6.8	\$40,175 (76,691)	\$44,719 (132,918)	4.2
Hospitalization costs	\$10,751 (30,724)	\$13,238 (57,878)	5.4	\$11,533 (33,020)	\$13,087 (56,826)	3.3
ED visit costs	\$10,362 (21,937)	\$11,747 (39,259)	4.4	\$11,145 (23,837)	\$11,666 (38,586)	1.6
Outpatient visit costs	\$16,612 (24,225)	\$20,139 (46,715)	9.5	\$17,496 (26,002)	\$19,966 (45,865)	6.6
Physician office visit costs	\$16,465 (24,126)	\$19,920 (46,587)	9.3	\$17,315 (25,911)	\$19,739 (45,726)	6.5
Home health care visit costs	\$4093 (13,272)	\$5018 (28,241)	4.2	\$3648 (13,064)	\$5008 (27,838)	6.3
Other outpatient visit costs	\$7228 (17,456)	\$9054 (35,523)	6.5	\$7127 (17,622)	\$8997 (34,786)	6.8
Pharmacy costs	\$2274 (4317)	\$835 (2124)	42.3	\$1504 (2946)	\$892 (2250)	23.3

^aCohorts 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 $\geq 5\%$. The weight was trimmed at 99% of the distribution. Counts are rounded to the nearest integer, while percentages are calculated from continuous weighted values.

^bFor 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: $|(P_{case} - P_{control})| / \sqrt{[(P_{case}(1 - P_{case}) + P_{control}(1 - P_{control})) / 2]}$.

^cEvaluated 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).

^dEvaluated during the 12-month baseline period, excluding the index date.

^ePer study design, all patients were prescribed ≥ 1 ADT during the baseline period.

^fMH-related HRU and costs were defined as visits with a primary or secondary MH diagnosis code.

^gCosts were inflated to 2022 USD using the US Medical Care consumer price index from the Bureau of Labor Statistics from the US Department of Labor.

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

Supplementary Table 6. Baseline Comorbidities^a of Weighted and Unweighted Cohorts: Adjunctive Cariprazine vs Adjunctive Aripiprazole

Characteristic	Unweighted cohorts			Weighted cohorts ^c		
	Adjunctive cariprazine (n=174)	Adjunctive aripiprazole (n=2931)	Std diff ^b (%)	Adjunctive cariprazine (n=174)	Adjunctive aripiprazole (n=2931)	Std diff ^b (%)
DSM-5 comorbidities, n (%)						
Anxiety disorders	131 (75.3)	2182 (74.4)	1.9	127 (72.8)	2188 (7406)	4.3
Sleep-wake disorders	71 (40.8)	957 (32.7)	17.0	65 (37.1)	969 (33.1)	8.5
Bipolar and related disorders	48 (27.6)	280 (9.6)	47.7	25 (14.2)	310 (10.6)	11.1
Substance-related and addictive disorders	48 (27.6)	580 (19.8)	18.4	41 (23.3)	593 (20.2)	7.5
Trauma- and stressor-related disorders	45 (25.9)	740 (25.2)	1.4	42 (24.1)	737 (25.1)	2.4
Breathing-related sleep disorder	38 (21.8)	471 (16.1)	14.8	29 (16.8)	478 (16.3)	1.4
Other conditions that may require a focus of clinical attention	31 (17.8)	622 (21.2)	8.6	29 (16.8)	617 (21.1)	11.0
Obsessive-compulsive and related disorders	13 (7.5)	103 (3.5)	17.4	9 (4.9)	109 (3.7)	5.8
Schizophrenia spectrum and other psychotic disorders	7 (4.0)	67 (2.3)	10.0	5 (2.6)	69 (2.4)	1.5
Other mental disorders	6 (3.4)	80 (2.7)	4.2	4 (2.5)	80 (2.7)	1.7
Feeding and eating disorders	5 (2.9)	66 (2.3)	3.9	7 (3.9)	67 (2.3)	9.5
Parasomnia disorders	4 (2.3)	73 (2.5)	1.3	3 (1.8)	76 (2.6)	5.1
Neurocognitive disorders	4 (2.3)	57 (1.9)	2.5	2 (1.2)	58 (2.0)	6.1
Personality disorders	2 (1.1)	70 (2.4)	9.4	2 (1.4)	71 (2.4)	7.7
Medication-induced movement disorders and other adverse effects of medication	2 (1.1)	16 (0.5)	6.6	2 (1.0)	16 (0.5)	5.1
Somatic symptom and related disorders	0 (0.0)	33 (1.1)	15.1	0 (0.0)	34 (1.2)	15.3
Elixhauser comorbidities, n (%)						
Hypertension	63 (36.2)	996 (34.0)	4.7	63 (36.1)	998 (34.1)	4.3
Obesity	49 (28.2)	727 (24.8)	7.6	49 (28.2)	731 (24.9)	7.3
Drug abuse	28 (16.1)	260 (8.9)	22.0	28 (16.2)	265 (9.0)	21.6
Chronic pulmonary disease	26 (14.9)	418 (14.3)	1.9	26 (14.7)	417 (14.2)	1.3
Hypothyroidism	25 (14.4)	398 (13.6)	2.3	29 (16.9)	400 (13.6)	9.1
Diabetes	25 (14.4)	358 (12.2)	6.3	24 (13.7)	362 (12.4)	4.1
Alcohol abuse	22 (12.6)	315 (10.7)	5.9	16 (9.2)	320 (10.9)	5.7
Cardiac arrhythmias	20 (11.5)	265 (9.0)	8.1	20 (11.8)	270 (9.2)	8.3
Fluid and electrolyte disorders	16 (9.2)	204 (7.0)	8.2	14 (8.0)	204 (6.9)	4.2
Rheumatoid arthritis/collagen vascular disease	14 (8.0)	151 (5.2)	11.7	11 (6.3)	156 (5.3)	4.0
Deficiency anemias	8 (4.6)	179 (6.1)	6.7	7 (3.8)	177 (6.1)	10.2
Psychoses	7 (4.0)	65 (2.2)	10.4	5 (2.6)	67 (2.3)	2.0

Liver disease	7 (4.0)	147 (5.0)	4.8	5 (3.0)	148 (5.1)	10.7
Other neurologic disorder	6 (3.4)	122 (4.2)	3.7	3 (1.6)	123 (4.2)	15.5
Weight loss	5 (2.9)	61 (2.1)	5.1	4 (2.5)	64 (2.2)	2.3
Coagulopathy	4 (2.3)	41 (1.4)	6.7	2 (1.2)	40 (1.4)	1.7
Renal failure	4 (2.3)	44 (1.5)	5.8	6 (3.5)	44 (1.5)	12.8
Congestive heart failure	3 (1.7)	29 (1.0)	6.4	3 (1.6)	29 (1.0)	5.1
Solid tumor without metastasis	3 (1.7)	84 (2.9)	7.6	1 (0.8)	82 (2.8)	14.9
Peripheral vascular disorders	3 (1.7)	41 (1.4)	2.6	3 (1.5)	42 (1.4)	0.3
Valvular disease	2 (1.1)	66 (2.3)	8.5	3 (2.0)	67 (2.3)	2.2
HIV/AIDS	2 (1.1)	18 (0.6)	5.7	3 (1.6)	18 (0.6)	9.3
Peptic ulcer disease	1 (0.6)	23 (0.8)	2.6	1 (0.8)	23 (0.8)	0.2
Blood loss anemia	1 (0.6)	30 (1.0)	5.0	1 (0.4)	30 (1.0)	7.6
Metastatic cancer	1 (0.6)	11 (0.4)	2.9	1 (0.7)	11 (0.4)	5.1
Paralysis	0 (0.0)	13 (0.4)	9.4	0 (0.0)	13 (0.4)	9.5

^aEvaluated during the 12-month baseline period, excluding the index date.

^bFor 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: $|P_{case} - P_{control}| / \sqrt{[(P_{case}(1 - P_{case}) + P_{control}(1 - P_{control})) / 2]}$.

^cCohorts 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 $\geq 5\%$. The weight was trimmed at 99% of the distribution. Counts are rounded to the nearest integer, while percentages are calculated from continuous weighted values.

DSM-5, *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition*; ED, emergency department; IPTW, inverse probability of treatment weighting; MDD, major depressive disorder; Std diff, standardized difference.