Original Research

Health Care Cost in Patients With Schizophrenia Treated With Brexpiprazole Versus Other Oral Atypical Antipsychotic Therapy☆

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ABSTRACT

Purpose: Brexpiprazole is an oral atypical antipsychotic (OAA) for the treatment of schizophrenia (SCZ). This study compared all-cause and psychiatric inpatient hospitalization and medical costs in adult patients with SCZ newly treated with brexpiprazole versus other US Food and Drug Administration—approved OAAs in a real-world setting.

Methods: This retrospective cohort study analyzed data from: (1) the IBM MarketScan Commercial and Medicare Supplemental databases, and the MarketScan Multi-State Medicaid database; and (2) the de-identified Optum Clinformatics Datamart. Adult patients were identified if they had SCZ and initiated either brexpiprazole or another OAA during the study identification period (July 1, 2015, to September 30, 2016, for MarketScan Commercial and Medicare Supplemental and for Optum; July 1, 2015, to June 30, 2016, for MarketScan Multi-State Medicaid) and had ≥12 months of continuous enrollment before (baseline) and after (follow-up) the first treatment date. Linear regression analyses were performed to test associations between treatment groups (brexpiprazole vs another OAA) and costs (total and medical); negative binomial regression models were used to estimate number of hospitalizations per year, adjusting for baseline

characteristics and medication adherence to index treatment during the 12-month follow-up.

Findings: The final study sample consisted of 6254 patients with SCZ: 176 initiated brexpiprazole; 391, ziprasidone; 453, paliperidone; 523, lurasidone; 786, aripiprazole; 1234, quetiapine; 1264, olanzapine; and 1427, risperidone. Controlling for baseline characteristics and medication adherence, the adjusted number of hospitalizations (both all-cause and psychiatric), all-cause total costs, and all-cause medical costs did not differ across groups. Brexpiprazole users had the lowest mean psychiatric costs among all OAA users ($12,013; 95% bootstrap CI, 7488—16,538). Compared with brexpiprazole users, paliperidone (incidence rate ratio [95% CI], 1.52 [1.05—2.19]; $P = 0.027$) and quetiapine (incidence rate ratio [95% CI], 1.47 [1.04—2.07]; $P = 0.029$) users had more psychiatric hospitalizations per year. Paliperidone had higher psychiatric costs than brexpiprazole (total, $32,066 [95% bootstrap CI, 28,779—35,353] vs $23,851 [18,907—28,795]; medical, $19,343 [16,294—22,392] vs $12,013 [7488—16,538]). Psychiatric medical costs were also $6744 higher in olanzapine users (95% bootstrap CI, 1694—11,795; $P = 0.009$) than in brexpiprazole users.

Implications: Patients with SCZ treated with brexpiprazole had fewer psychiatric hospitalizations and lower psychiatric costs than those treated with paliperidone. Differences in the number of all-cause hospitalizations and medical costs among treatments were not statistically significant. Although treatment decisions are driven by a number of factors (eg, clinical circumstances and drug costs), choice of OAA may affect health care costs. (*Clin Ther.* 2020;42:77–93) © 2019 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Key words: antipsychotic, cost, hospitalization, schizophrenia, secondary data.

INTRODUCTION

Schizophrenia (SCZ) is a disabling mental disorder that affects ~1.1% of adults in the United States.[1] The financial burden of treating and managing SCZ is high, with overall costs estimated at $156 billion in 2013, including $37.7 billion in direct health care costs.[2] SCZ is one of the most costly diseases in the United States, with $44,773 spent per patient annually in 2013. Relapsed patients incur 3 to 4 times higher health care costs than those who do not relapse, mainly due to the costs of hospitalizations.[3] Thus, providing effective treatment that reduces utilization is one important way to decrease cost.

Oral atypical antipsychotics (OAAs) are the cornerstone of current treatment for SCZ. These medications help many patients manage their symptoms effectively and can contribute to reduced utilization; however, the choice of OAAs in an individual patient is complicated. The American Psychiatric Association recommends OAAs as first-line treatment.[4]

Brexpiprazole is an OAA that was approved in the United States in 2015 as monotherapy to treat SCZ in adults. In a recent cost-effectiveness analysis, brexpiprazole was estimated to be less costly and more effective than cariprazine and lurasidone for preventing relapses and hospitalizations for patients with SCZ.[5] However, the inputs for the analysis were from randomized trials, and we found no studies comparing utilization and cost in patients treated with brexpiprazole versus other OAAs using real-world data.

The current study used multiple claims databases to compare brexpiprazole with other US Food and Drug Administration–approved OAAs to better understand the effects of antipsychotic choice on hospitalization and medical costs in a real-world setting. The goal is to help reduce the economic burden of SCZ on the US health care system.

MATERIALS AND METHODS
Data Sources and Study Design

This retrospective cohort analysis used administrative claims data from the IBM MarketScan Commercial and Medicare Supplemental databases and the MarketScan Multi-State Medicaid database (IBM Corporation, Armonk, New York), as well as de-identified Optum Clinformatics Datamart. All data were compliant with the Health Insurance Portability and Accountability Act of 1996. As such, institutional review board approval was not required for this study. Each database was analyzed separately, including separate data cleaning and study population cohort identification, but were combined for the final analysis.

The MarketScan Commercial and Medicare Supplemental databases represent health services of >43.6 million employees, dependents, and retirees in the United States with primary or Medicare supplemental coverage through privately insured fee-for-service, point-of-service, or capitated health plans. The databases include enrollment information and claims with health care utilization information (eg, inpatient and outpatient services, prescription drug claims). The MarketScan Multi-State Medicaid database contains demographic characteristics and health care records of >44 million Medicaid enrollees from multiple states. Optum data cover >10 years of patient experience and contain de-identified claims and clinical data from multiple health plans and health care providers for >150 million people.

Sample Selection

Adult patients with SCZ (existing or newly diagnosed) were identified by the presence of at least 1 inpatient or 2 outpatient claims for schizophrenic disorders (*International Classification of Diseases, Ninth Revision, Clinical Modification* code, 295.xx, excluding 295.4x and 295.7x; or *International Classification of Diseases, Tenth Revision, Clinical Modification* code, F20.x, excluding F20.81x) in any

diagnosis field of a claim during the study period. The periods differed between databases: July 1, 2014, to September 30, 2017, for MarketScan Commercial and Medicare Supplemental; July 1, 2014, to June 30, 2017, for MarketScan Multi-State Medicaid; and July 1, 2014, to September 30, 2017, for Optum.

Among patients with SCZ, 8 mutually exclusive cohorts were identified: the brexpiprazole cohort and the other individual OAA (ie, aripiprazole, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone) cohorts. Patients were identified based on having at least 1 claim for either brexpiprazole or another US Food and Drug Administration–approved OAA single agent during the study identification period (July 1, 2015, to September 30, 2016, for MarketScan Commercial and Medicare Supplemental and for Optum; July 1, 2015, to June 30, 2016, for MarketScan Multi-State Medicaid); and with no claims for the index agent in the previous 12 months. The study index date was defined as the date of the first claim for the index

OAA (Figure 1). In addition, to ensure adequate sample size for the brexpiprazole cohort, these patients were identified first during the cohort identification.

Patients were also required to have one diagnosis for SCZ during the 12 months before (baseline period) or on the index date, as well as continuous enrollment before baseline and at least 12 months after the index date (follow-up period). Patients with SCZ were allowed to have other concomitant mental health diagnoses (eg, bipolar disorder, anxiety disorder, depression, schizoaffective disorder). The study design scheme is presented in Figure 1.

Patients who were treated with >1 antipsychotic therapy on the index date were excluded. In addition, patients were excluded if they had a claim for clozapine during the study period because clozapine is indicated for the treatment of severely ill patients with SCZ who have failed to respond adequately to standard antipsychotic therapy.[6–8] Due to incomplete data associated with the MarketScan Multi-State

Index date
(Start date of index OAA)

12-month baseline/washout period
(No index medication)

≥12-month follow-up period

7/1/14 Optum
7/1/14 MarketScan

7/1/15 Optum
7/1/15 MarketScan

Identification Period

9/30/16 Optum,
MarketScan C/MS;
6/30/16 MarketScan M

9/30/17 Optum,
MarketScan C/MS;
6/30/17 MarketScan M

C=commercial; MS=Medicare supplemental; M=Medicaid; OAA=oral atypical antipsychotic
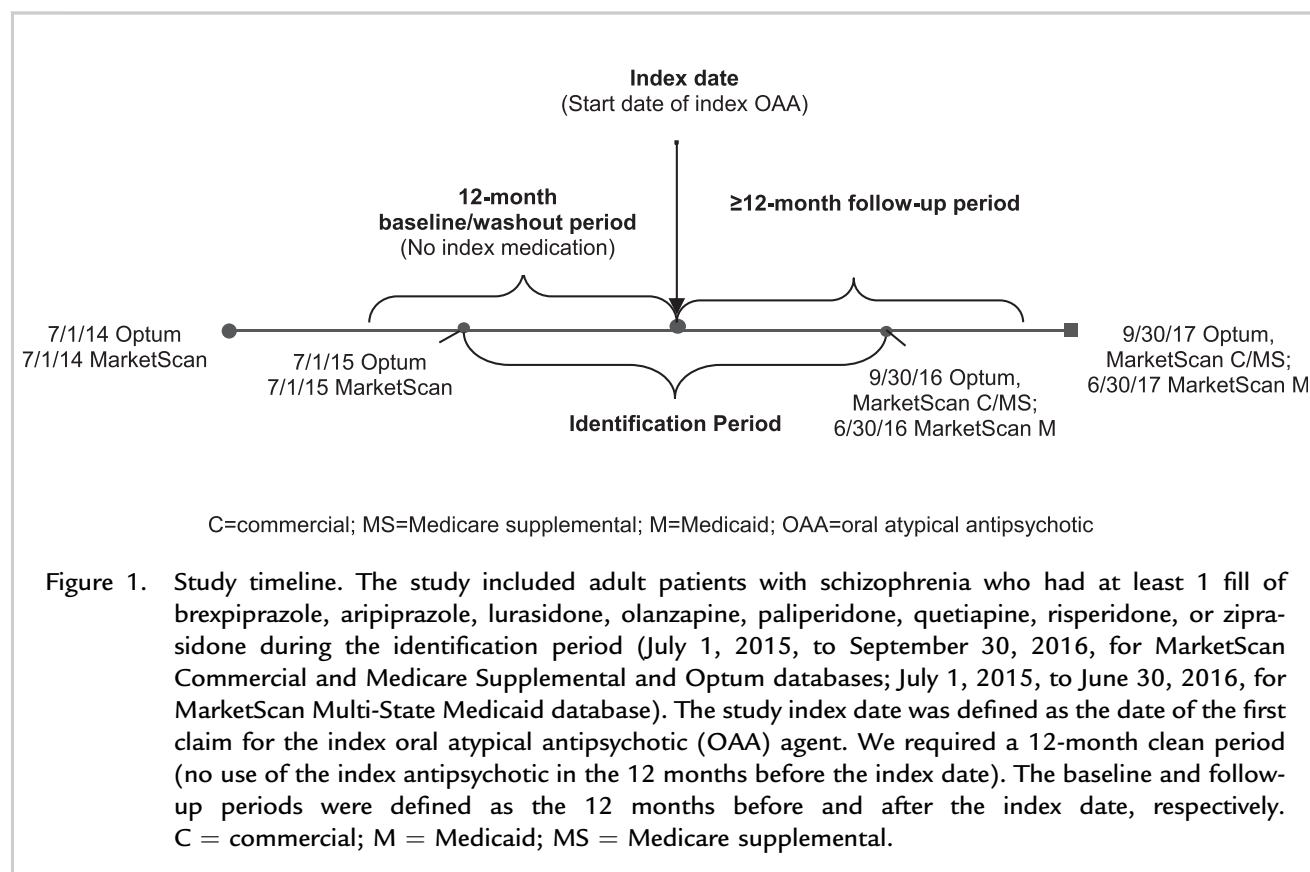
Figure 1. Study timeline. The study included adult patients with schizophrenia who had at least 1 fill of brexpiprazole, aripiprazole, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, or ziprasidone during the identification period (July 1, 2015, to September 30, 2016, for MarketScan Commercial and Medicare Supplemental and Optum databases; July 1, 2015, to June 30, 2016, for MarketScan Multi-State Medicaid database). The study index date was defined as the date of the first claim for the index oral atypical antipsychotic (OAA) agent. We required a 12-month clean period (no use of the index antipsychotic in the 12 months before the index date). The baseline and follow-up periods were defined as the 12 months before and after the index date, respectively. C = commercial; M = Medicaid; MS = Medicare supplemental.

Medicaid database, patients were excluded who were Medicare and Medicaid dual eligible, did not have pharmacy coverage or mental health coverage information, or had a capitated plan. To prevent including potential duplicate records, patients with the same age, sex, region, insurance type, index date, and index medication found in both the MarketScan and Optum databases were randomly removed from one of the databases.

Study Measures

Baseline measures included patient demographic characteristics (age, sex, and insurance), Charlson Comorbidity Index score,[9,10] number of Healthcare Cost and Utilization Project (HCUP) chronic conditions,[11] and number of psychiatric (anxiety, bipolar disorder, personality disorder, and substance abuse disorder) and nonpsychiatric (obesity, type 2 diabetes mellitus, hyperlipidemia, and hypertension) comorbidities; medication use (nonindex antipsychotics; psychiatric [antidepressants, antianxiety medications, sedatives or hypnotics, and mood stabilizers]; and nonpsychiatric [antidiabetic medications, lipid-lowering medications, and antihypertensive medications]), and emergency department (ED) and hospital utilization.

The health care utilization and costs were examined in the inpatient and outpatient settings. The study outcome measures of interest included all-cause hospitalizations, total costs including medical (which included inpatient and outpatient services but did not include outpatient pharmacy) and outpatient pharmacy costs, psychiatric hospitalization, and psychiatric costs during the follow-up period. Psychiatric hospitalization and costs were defined as those with a primary diagnosis of a mental disorder (*International Classification of Diseases, Ninth Revision, Clinical Modification* codes, 290.xx–311.xx; *International Classification of Diseases, Tenth Revision, Clinical Modification* codes, F01.xx–F99.xx).

Statistical Analysis

Descriptive statistics were performed to assess baseline differences between cohorts, including means, SDs, and relative frequencies and percentages for continuous and categorical data. In addition, χ^2 tests were used for categorical variables, and ANOVA or Kruskal–Wallis tests were performed for continuous variables, depending on the variable distributions.

Linear regression models were used to estimate total and medical costs, and negative binomial regression models were used to estimate number of inpatient hospitalizations per year. For cost outcomes, 95% bootstrap CIs were calculated by using the 2.5th and 97.5th percentiles of the 1000 bootstrap replications. All models were adjusted for baseline age groups, sex, insurance type, Charlson Comorbidity Index score, any psychiatric comorbidities, hyperlipidemia, hypertension, ED visits, hospitalizations, nonindex antipsychotic use, psychiatric medication use, and nonpsychiatric medication use.

In the absence of a single acceptable measure of SCZ severity available in administrative claims data, we used ED and hospital utilization as well as nonindex antipsychotic medication use as proxies for severity of SCZ. In addition, because previous studies suggest that suboptimal medication adherence levels are associated with poor health outcomes,[12–17] we adjusted for adherence to index treatment during the 12-month follow-up period. Medication adherence was measured by proportion of days covered (PDC). PDC was calculated as the number of available days of index therapy divided by 365.[18] The days' supply as reported on the prescription claim was used to calculate the PDC. Only statistically significant ($P < 0.05$) covariates are presented in the final models. Bootstrap 95% CIs and P values are also reported.

All costs were adjusted to 2017 US dollars using the medical care component of the Consumer Price Index. All data transformation and statistical analyses were performed by using SAS version 9.4 (SAS Institute, Inc, Cary, North Carolina).

RESULTS

Sample Selection and Baseline Characteristics

Of the 116,366 identified patients with SCZ during the study period (73,969 MarketScan; 42,397 Optum), 28,833 newly started an OAA in the identification period. After excluding those without at least 1 SCZ diagnosis before or on the index date, no continuous enrollment during baseline and follow-up, or not on OAA monotherapy, and who were aged <18 years, 6720 patients remained. Two possible duplicates were removed from each database. In addition, 174 clozapine users were removed. Patients who initiated

asenapine, loxapine, iloperidone, or cariprazine were further removed from the final sample due to small sample size (cutoff was <175 patients on a medication) (Figure 2). The final cohort of 6254 patients with SCZ included: 176 initiated brexpiprazole; 786, aripiprazole; 523, lurasidone; 1264, olanzapine; 453, paliperidone; 1234, quetiapine; 1427, risperidone; and 391, ziprasidone.

The mean (SD) age of the study population was 44.3 (16.6) years, although the groups differed significantly, with brexpiprazole users being the youngest (mean [SD] age, 39.5 [14.3] years) and quetiapine users the oldest (mean, 46.9 [16.8] years; $P < 0.001$). Male patients (53.7% overall) and Medicaid recipients (53.9% overall) comprised the majority of the OAA groups (Table I).

There were statistically significant group differences in clinical characteristics. The mean (SD) Charlson Comorbidity Index score was highest in quetiapine users (1.9 [2.5]) and lowest in paliperidone users (1.2 [1.9]), as were the number of HCUP chronic conditions ($P < 0.001$). The majority of patients had psychiatric comorbidities (81.4%), with depression being the most frequent overall (53.9%) (results not shown). More than one half of the patients had previous hospitalizations, with the highest rates in olanzapine users (63.9%) and the lowest in brexpiprazole users (45.5%) ($P < 0.001$). Medication use at baseline was common, with brexpiprazole users having the highest use of nonindex antipsychotic medication (95.5%) ($P < 0.001$) (Table I).

Medication Adherence, Health Care Utilization, and Costs During the 12-Month Follow-up Period

In the unadjusted analysis, there were some differences in utilization and costs across OAAs. Mean (SD) PDC ranged from 0.39 (0.35) in paliperidone users to 0.51 (0.36) in lurasidone users ($P < 0.001$). Ziprasidone users had the fewest office visits (all-cause, 9.5 [18.6]; psychiatric, 5.8 [17.1]) but the most ED visits (2.33 [5.0]; 0.60 [1.70], respectively) (all, $P < 0.05$). Unadjusted all-cause hospitalization did not differ across OAAs. Brexpiprazole users had the fewest psychiatric hospitalizations (0.52 [1.0]; $P = 0.013$) (Table II). Unadjusted all-cause medical costs and inpatient costs did not differ. Brexpiprazole users had the lowest mean (SD) annual psychiatric care costs ($13,888

[$29,968]) and the lowest psychiatric inpatient costs ($9218 [$26,551]) (both, $P < 0.001$) but the highest all-cause pharmacy costs ($15,910 [$12,864]; $P < 0.001$). Paliperidone users had the highest total all-cause costs ($46,522 [$48,967]; $P = 0.004$) (Table III).

Controlling for baseline characteristics and medication adherence, the adjusted number of hospitalizations (both all-cause and psychiatric) and all-cause total and medical costs did not differ across groups. Brexpiprazole users had the lowest mean psychiatric costs among all OAA users ($12,013; 95% bootstrap CI, 7488−16,538). Paliperidone and quetiapine users had more psychiatric hospitalizations per year than brexpiprazole users (incidence rate ratio [95% CI], 1.52 [1.05−2.19], $P = 0.027$; 1.47 [1.04−2.07], $P = 0.029$). Paliperidone had higher psychiatric costs than brexpiprazole (total [95% bootstrap CI], $32,066 [28,779−35,353) vs $23,851 [18,907−28,795]; medical, $19,343 [16,294−22,392] vs $12,013 [7488−16,538]). Psychiatric costs were also $6744 higher in olanzapine users (95% bootstrap CI, 1694−11,795; $P = 0.009$) than in brexpiprazole users. There were no statistically significant differences in all-cause hospitalization or total and medical costs between brexpiprazole users and users of other OAAs (Tables IV and V).

DISCUSSION

OAAs differ in efficacy and tolerability.[19−21] Brexpiprazole is one of the more recently approved atypical antipsychotic agents for the treatment of SCZ, and the efficacy and safety of brexpiprazole have been reported in short- and long-term studies.[22−25] Due to the relatively recent approval of brexpiprazole, comparison studies between brexpiprazole and other OAAs in SCZ are limited.[22−26]

In this study combining 2 large claims databases, we found that in patients with SCZ, choice of OAAs had an impact on psychiatric health care utilization and costs. Brexpiprazole users had a statistically significantly lower number of psychiatric hospitalizations per year compared with paliperidone users. Brexpiprazole use was also associated with the lowest psychiatric costs among the OAAs. Differences among the OAAs were not large enough to observe statistically significant differences in all-cause health care utilization. This was also true for the differences
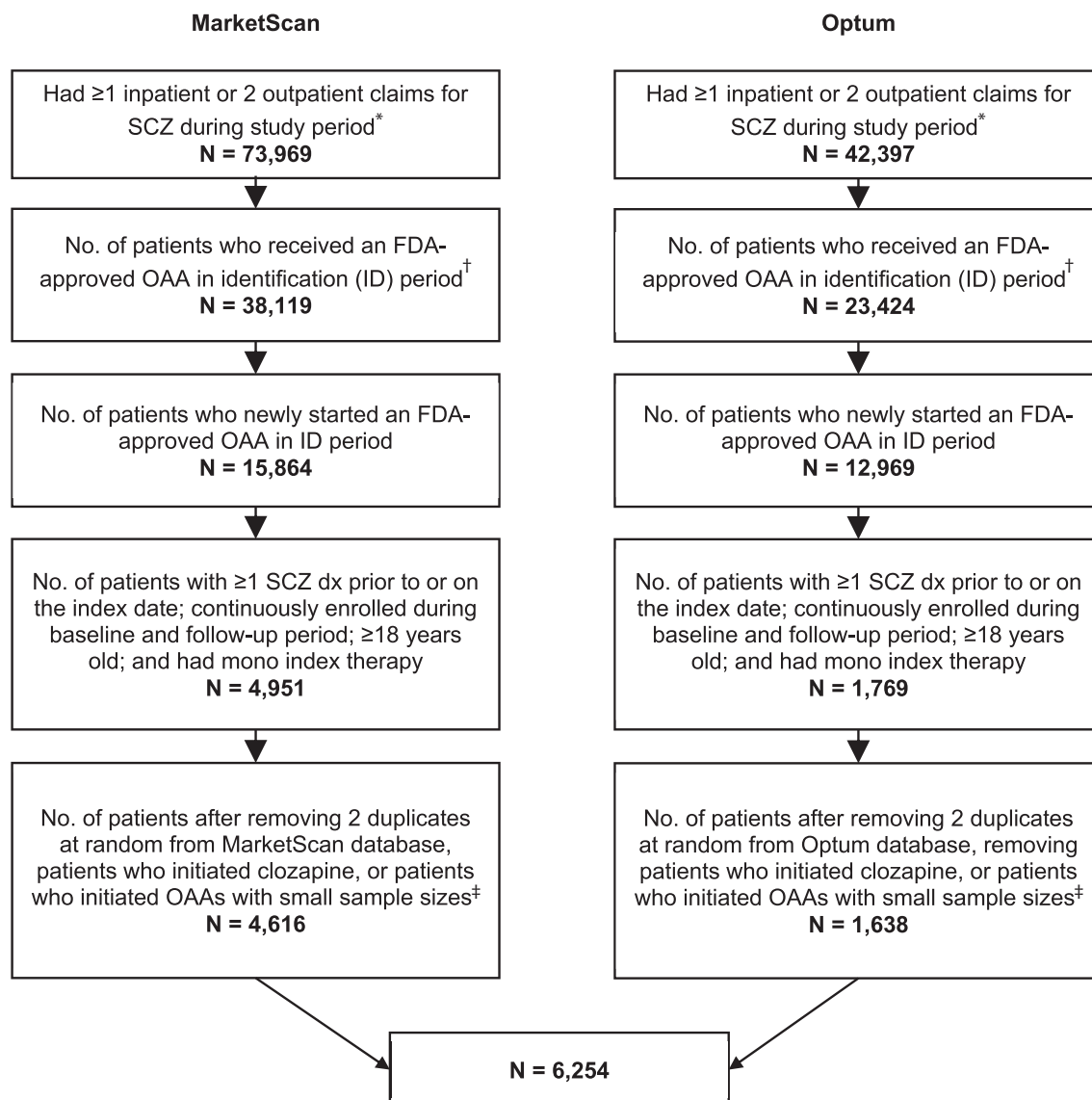
Figure 2. Patient attrition. Across the databases, there were 116,366 identified patients with schizophrenia (SCZ) during the study period. Of these, 28,833 newly started an oral atypical antipsychotic (OAA) in the identification (ID) period. After excluding those without at least 1 SCZ diagnosis before or on the index date, no continuous enrollment during baseline and follow-up, or not on OAA monotherapy, and who were aged <18 years, 6720 patients remained. Two possible duplicates were removed from each database. In addition, 174 clozapine users were removed. Patients who initiated asenapine, loxapine, iloperidone, or cariprazine were further removed from the final sample due to small sample size (cutoff was <175 patients on a medication). The final cohort consisted of 6254 patients with SCZ. *Study period: July 1, 2014, to September 30, 2017, for the MarketScan Commercial/Medicare Supplemental and Optum databases; July 1, 2014, to June 30, 2017, for the MarketScan Multi-State Medicaid database. [†]Identification period: July 1, 2015, to September 30, 2016, MarketScan Commercial/Medicare Supplemental database; Optum database, July 1, 2015, to June 30, 2016, for MarketScan Multi-State Medicaid database. [‡]Less than 175 patients (asenapine, 138; loxapine, 74; iloperidone, 39; cariprazine, 37). FDA = US Food and Drug Administration.

Table I. Baseline characteristics.

Characteristic	Brexpiprazole (n = 176 [2.8%])	Aripiprazole (n = 786 [12.6%])	Lurasidone (n = 523 [8.4%])	Olanzapine (n = 1264 [20.2%])	Paliperidone (n = 453 [7.2%])	Quetiapine (n = 1234 [19.7%])	Risperidone (n = 1427 [22.8%])	Ziprasidone (n = 391 [6.3%])	All (N = 6254 [100%])	P
Age, mean (SD) [median], y	39.5 (14.3) [39]	43.2 (17.0) [43]	42.7 (15.5) [44]	44.5 (16.8) [45]	41.2 (15.1) [39]	46.9 (16.8) [48]	45.1 (17.2) [46]	42.2 (14.6) [44]	44.3 (16.6) [45]	<0.001
Female, no. (%)	93 (52.8)	363 (46.2)	278 (53.2)	563 (44.5)	184 (40.6)	592 (48.0)	628 (44.0)	197 (50.4)	2898 (46.3)	<0.001
Insurance type, no. (%)										
Commercial	62 (35.2)	233 (29.6)	148 (28.3)	279 (22.1)	86 (19.0)	201 (16.3)	299 (21.0)	84 (21.5)	1392 (22.3)	<0.001
Medicaid	80 (45.5)	325 (41.3)	252 (48.2)	687 (54.4)	283 (62.5)	727 (58.9)	774 (54.2)	241 (61.6)	3369 (53.9)	
Medicare	34 (19.3)	228 (29.0)	123 (23.5)	298 (23.6)	84 (18.5)	306 (24.8)	354 (24.8)	66 (16.9)	1493 (23.9)	
Charlson Comorbidity Index score, mean (SD) [median]	1.3 (2.0) [0]	1.5 (2.2) [0]	1.6 (2.3) [1]	1.5 (2.1) [1]	1.2 (1.9) [0]	1.9 (2.5) [1]	1.5 (2.3) [1]	1.7 (2.4) [1]	1.6 (2.3) [1]	<0.001
No. of chronic conditions, mean (SD) [median]	4.3 (2.5) [4]	4.3 (2.7) [4]	4.5 (2.5) [4]	4.4 (2.5) [4]	4.2 (2.4) [4]	4.7 (2.6) [5]	4.2 (2.6) [4]	4.6 (2.6) [4]	4.4 (2.6) [4]	<0.001
Psychiatric comorbidities,[*] no. (%)	139 (79.0)	619 (78.8)	422 (80.7)	1028 (81.3)	358 (79.0)	1029 (83.4)	1151 (80.7)	342 (87.5)	5088 (81.4)	0.007
Nonpsychiatric comorbidities,[†] no. (%)	115 (65.3)	464 (59.0)	349 (66.7)	778 (61.6)	260 (57.4)	837 (67.8)	864 (60.5)	256 (65.5)	3923 (62.7)	<0.001
Any baseline ED visits, no. (%)	104 (59.1)	422 (53.7)	301 (57.6)	772 (61.1)	266 (58.7)	776 (62.9)	850 (59.6)	249 (63.7)	3740 (59.8)	0.003
Any baseline inpatient hospitalization, no. (%)	80 (45.5)	440 (56.0)	274 (52.4)	808 (63.9)	236 (52.1)	680 (55.1)	889 (62.3)	221 (56.5)	3628 (58.0)	<0.001
Nonindex antipsychotic medications, no. (%)	168 (95.5)	585 (74.4)	427 (81.6)	851 (67.3)	404 (89.2)	816 (66.1)	803 (56.3)	297 (76.0)	4351 (69.6)	<0.001
Psychiatric medications,[‡] no. (%)	164 (93.2)	581 (73.9)	453 (86.6)	915 (72.4)	364 (80.4)	925 (75.0)	891 (62.4)	300 (76.7)	4593 (73.4)	<0.001
Nonpsychiatric medications,[§] no. (%)	107 (60.8)	376 (47.8)	291 (55.6)	619 (49.0)	219 (48.3)	674 (54.6)	675 (47.3)	209 (53.5)	3170 (50.7)	<0.001

ED = emergency department.

[*] Bipolar disorder, depression, anxiety, personality disorder, or substance abuse disorders.

[†] Obesity, type 2 diabetes mellitus, hyperlipidemia, and hypertension.

[‡] Mood stabilizers, antidepressants, antianxiety medications, sedatives, or hypnotics.

[§] Antidiabetic medications, lipid-lowering medications, and antihypertensive medications.

Table II. Health care utilization during the 12-month follow-up period.

Variable	Brexpiprazole (n = 176 [2.8%])	Aripiprazole (n = 786 [12.6%])	Lurasidone (n = 523 [8.4%])	Olanzapine (n = 1264 [20.2%])	Paliperidone (n = 453 [7.2%])	Quetiapine (n = 1234 [19.7%])	Risperidone (n = 1427 [22.8%])	Ziprasidone (n = 391 [6.3%])	All (N = 6254 [100%])	P
All-cause utilization										
No. of office visits, mean (SD) [median]	16.3 (18.7) [11]	12.8 (18.7) [7]	15.9 (22.4) [8]	10.7 (18.5) [4]	14.0 (21.0) [6]	10.3 (18.7) [4]	9.8 (16.5) [4]	9.5 (18.6) [4]	11.4 (18.8) [5]	<0.001
No. of ED visits, mean (SD)	1.97 (7.7)	1.95 (7.7)	1.94 (5.2)	1.85 (5.1)	1.77 (5.1)	2.20 (5.3)	1.86 (4.8)	2.33 (5.0)	1.97 (5.6)	<0.001*
Any inpatient hospitalization, no. (%)	68 (38.6)	313 (39.8)	206 (39.4)	520 (41.1)	205 (45.3)	515 (41.7)	569 (39.9)	181 (46.3)	2577 (41.2)	0.175
No. of inpatient hospitalizations, mean (SD)	0.78 (1.3)	0.93 (2.0)	1.06 (2.5)	1.10 (2.3)	1.13 (2.0)	1.06 (2.1)	0.97 (2.1)	1.26 (2.4)	1.04 (2.2)	0.124*
Inpatient hospital stays among patients with hospitalization										
No. of days	68	313	206	520	205	515	569	181	2577	
Mean (SD) [median], d	15.9 (19.3) [9]	21.6 (35.3) [11]	22.0 (30.0) [11]	21.3 (27.8) [11]	23.5 (32.4) [12]	18.8 (26.0) [10]	19.1 (24.5) [10]	18.9 (20.7) [12]	20.3 (27.8) [11]	0.210
Psychiatric† utilization										
No. of psychiatric office visits, mean (SD) [median]	9.6 (13.7) [4]	8.0 (16.8) [3]	10.3 (20.1) [3]	7.1 (17.4) [1]	10.7 (20.0) [3]	6.3 (16.8) [1]	6.0 (14.6) [1]	5.8 (17.1) [1]	7.3 (17.0) [1]	<0.001
No. of psychiatric ED visits, mean (SD)	0.24 (1.5)	0.47 (1.8)	0.44 (1.6)	0.60 (2.9)	0.49 (1.6)	0.52 (1.7)	0.48 (1.7)	0.60 (1.7)	0.51 (2.0)	0.012*
No. of psychiatric inpatient hospitalizations, mean (SD)	0.52 (1.0)	0.63 (1.5)	0.73 (2.2)	0.79 (2.0)	0.89 (1.8)	0.69 (1.7)	0.67 (1.7)	0.86 (1.8)	0.72 (1.8)	0.013*
Inpatient hospital stays among patients with hospitalization										
No. of days	50	233	152	396	166	348	420	136	1901	
Mean (SD) [median], d	18.1 (20.7) [11]	23.0 (38.5) [11]	22.9 (26.5) [12]	22.3 (27.4) [12]	24.9 (31.4) [15]	19.4 (22.8) [13]	19.4 (23.3) [11]	19.6 (20.3) [13]	21.2 (27.1) [12]	0.195

ED = emergency department.

* Kruskal–Wallis test.

† Claims with a primary diagnosis of any mental disorder (*International Classification of Diseases, Ninth Revision, Clinical Modification* codes, 290.xx–311.xx; *International Classification of Diseases, Tenth Revision, Clinical Modification* codes, F01.xx–F99.xx).

Table III. Health care costs during the 12-month follow-up period.

Variable	Brexpiprazole (n = 176 [2.8%])	Aripiprazole (n = 786 [12.6%])	Lurasidone (n = 523 [8.4%])	Olanzapine (n = 1264 [20.2%])	Paliperidone (n = 453 [7.2%])	Quetiapine (n = 1234 [19.7%])	Risperidone (n = 1427 [22.8%])	Ziprasidone (n = 391 [6.3%])	All (N = 6254 [100%])	P
All-cause costs										
Total costs, mean (SD) [median]	$41,186 (46,410) [27,808]	$40,235 (79,936) [19,749]	$44,304 (62,012) [26,993]	$37,690 (55,431) [17,517]	$46,522 (48,967) [30,713]	$38,392 (61,680) [18,261]	$34,539 (56,022) [15,204]	$42,201 (62,570) [20,205]	$39,003 (60,826) [19,948]	0.004
Medical costs*	$25,275 (43,031) [9774]	$29,852 (76,047) [8191]	$29,249 (59,609) [10,645]	$31,273 (53,266) [11,274]	$29,953 (44,637) [11,490]	$31,717 (59,499) [10,790]	$28,527 (54,276) [9018]	$35,640 (61,240) [13,298]	$30,395 (58,303) [10,327]	0.408
Total outpatient medical costs	$12,765 (28,001) [4529]	$11,377 (39,396) [4182]	$12,352 (24,004) [4676]	$9363 (18,210) [4100]	$10,782 (20,483) [4403]	$11,250 (22,751) [4518]	$8437 (19,015) [3398]	$10,066 (16,583) [4694]	$10,269 (23,785) [4135]	0.005
Total inpatient medical costs†	$12,511 (29,239) [0]	$18,475 (60,812) [0]	$16,897 (44,053) [0]	$21,911 (46,392) [0]	$19,171 (36,414) [0]	$20,467 (51,344) [0]	$20,091 (49,327) [0]	$25,574 (56,264) [51]	$20,126 (49,582) [0]	0.054
Total outpatient pharmacy costs, mean (SD) [median]	$15,910 (12,864) [13,268]	$10,383 (12,675) [6434]	$15,055 (14,771) [11,775]	$6417 (12,591) [1899]	$16,569 (17,099) [12,692]	$6675 (11,530) [2349]	$6011 (11,363) [1881]	$6561 (9949) [3119]	$8608 (13,095) [3715]	<0.001
Psychiatric‡ costs										
Total psychiatric costs, mean (SD) [median]	$26,609 (32,279) [15,017]	$21,593 (29,387) [10,149]	$27,332 (32,150) [16,117]	$22,879 (40,661) [6346]	$34,320 (36,067) [22,772]	$18,062 (32,741) [5150]	$18,198 (32,420) [4860]	$22,378 (34,311) [8793]	$21,974 (34,596) [8973]	<0.001
Psychiatric costs* (excluding psychiatric injectables), mean (SD) [median]	$13,888 (29,968) [1721]	$14,060 (28,057) [2057]	$16,122 (30,268) [2418]	$19,099 (39,243) [2564]	$20,543 (33,162) [5519]	$14,526 (31,387) [1667]	$14,775 (31,265) [1718]	$18,954 (32,883) [4469]	$16,277 (32,877) [2271]	<0.001
Total psychiatric outpatient medical costs (excluding psychiatric injectables)	$4670 (12,414) [1186]	$3964 (10,414) [1125]	$5536 (13,192) [1493]	$4497 (12,317) [1065]	$6071 (14,912) [1675]	$4897 (17,262) [881]	$3737 (13,779) [893]	$5144 (13,214) [1412]	$4582 (13,878) [1067]	0.026

Table III.   (Continued)

Variable	Brexpiprazole (n = 176 [2.8%])	Aripiprazole (n = 786 [12.6%])	Lurasidone (n = 523 [8.4%])	Olanzapine (n = 1264 [20.2%])	Paliperidone (n = 453 [7.2%])	Quetiapine (n = 1234 [19.7%])	Risperidone (n = 1427 [22.8%])	Ziprasidone (n = 391 [6.3%])	All (N = 6254 [100%])	P
Total psychiatric inpatient medical costs, mean (SD) [median]	$9218 (26,551) [0]	$10,096 (24,543) [0]	$10,585 (26,606) [0]	$14,602 (35,037) [0]	$14,472 (28,939) [0]	$9629 (24,532) [0]	$11,038 (27,250) [0]	$13,809 (27,509) [0]	$11,695 (28,324) [0]	<0.001
Mental health —related medication costs§ (including psychiatric injectables), mean (SD) [median]	$12,721 (11,028) [10,147]	$7532 (7852) [4960]	$11,210 (9354) [9639]	$3780 (7302) [789]	$13,777 (11,230) [10,537]	$3536 (6803) [853]	$3423 (6184) [646]	$3424 (5607) [1305]	$5697 (8390) [1833]	<0.001

*Total inpatient and outpatient service costs; excludes outpatient pharmacy costs.

† Including costs incurred in a hospital, skilled nursing facility, or nursing home care.

‡ Claims with a primary diagnosis of any mental disorder

(International Classification of Diseases, Ninth Revision, Clinical Modification codes, 290.xx–311.xx; International Classification of Diseases, Tenth Revision, Clinical Modification codes, F01.xx–F99.xx) and costs of mental health–related treatments.

§ Including either long-acting injectable therapies or oral formulations.

Table IV. Adjusted estimates of health care utilization.

Parameter	Negative Binomial Models			
	No. of All-cause Inpatient Hospitalizations per Year		No. of Psychiatric* Inpatient Hospitalizations per Year	
	IRR (95% CI)	P	IRR (95% CI)	P
Age group, y				
18–30 vs ≥65	1.55 (1.27–1.89)	<0.001	2.79 (2.16–3.61)	<0.001
31–64 vs ≥65	1.46 (1.23–1.73)	<0.001	2.40 (1.91–3.02)	<0.001
Female vs male	0.83 (0.76–0.91)	<0.001	0.79 (0.71–0.88)	<0.001
Insurance type				
Medicaid vs commercial	1.21 (1.07–1.36)	0.002	1.18 (1.02–1.37)	0.022
Medicare vs commercial	1.14 (0.97–1.33)	0.103	1.07 (0.88–1.29)	0.502
Charlson Comorbidity Index score	1.10 (1.08–1.12)	<0.001	—	NS[†]
Any psychiatric comorbidities[‡] (Y vs N)	—	NS[†]	—	NS[†]
Hyperlipidemia (Y vs N)	—	NS[†]	—	NS[†]
Hypertension (Y vs N)	—	NS[†]	—	NS[†]
Any baseline ED visits (Y vs N)	1.47 (1.34–1.62)	<0.001	1.54 (1.37–1.73)	<0.001
Any baseline inpatient hospitalization (Y vs N)	2.94 (2.68–3.24)	<0.001	3.61 (3.21–4.06)	<0.001
Baseline nonindex antipsychotic medications (Y vs N)	1.29 (1.17–1.43)	<0.001	1.54 (1.36–1.75)	<0.001
Baseline psychiatric medication[§] use (Y vs N)	1.22 (1.10–1.36)	<0.001	1.29 (1.13–1.48)	<0.001
Baseline nonpsychiatric medication[‖] use (Y vs N)	—	NS[†]	—	NS[†]
PDC of index medication (range, 0–1)	0.46 (0.40–0.52)	<0.001	0.37 (0.32–0.43)	<0.001
	IRR (95% CI)	P	IRR (95% CI)	P
Index treatment				
Aripiprazole vs brexpiprazole	1.21 (0.90–1.61)	0.200	1.37 (0.96–1.96)	0.080
Lurasidone vs brexpiprazole	1.31 (0.97–1.77)	0.073	1.45 (1.01–2.09)	0.047
Olanzapine vs brexpiprazole	1.22 (0.92–1.61)	0.169	1.40 (0.99–1.97)	0.054
Paliperidone vs brexpiprazole	1.30 (0.96–1.76)	0.090	1.52 (1.05–2.19)	0.027
Quetiapine vs brexpiprazole	1.32 (1.00–1.75)	0.052	1.47 (1.04–2.07)	0.029
Risperidone vs brexpiprazole	1.17 (0.89–1.55)	0.266	1.30 (0.92–1.83)	0.135
Ziprasidone vs brexpiprazole	1.31 (0.96–1.78)	0.084	1.47 (1.01–2.14)	0.045
	Adjusted No. of All-cause Hospitalizations per year (95% CI)		Adjusted No. of Psychiatric* Hospitalizations per year (95% CI)	
Index treatment	P = 0.358		P = 0.347	
Aripiprazole	0.751 (0.666–0.847)		0.484 (0.417–0.561)	
Lurasidone	0.817 (0.707–0.945)		0.511 (0.428–0.609)	
Olanzapine	0.756 (0.689–0.830)		0.494 (0.441–0.553)	
Paliperidone	0.808 (0.694–0.940)		0.535 (0.446–0.641)	
Quetiapine	0.821 (0.748–0.902)		0.517 (0.460–0.582)	

Table IV. (Continued)

	Adjusted No. of All-cause Hospitalizations per year (95% CI)	Adjusted No. of Psychiatric* Hospitalizations per year (95% CI)
Risperidone	0.729 (0.666–0.798)	0.458 (0.410–0.512)
Ziprasidone	0.816 (0.695–0.957)	0.518 (0.426–0.629)
Brexpiprazole	0.622 (0.477–0.810)	0.352 (0.255–0.488)

ED = emergency department; IRR = incidence rate ratio; N = no; NS = not significant; PDC = proportion of days covered; Y = yes.
*Claims with a primary diagnosis of any mental disorder (*International Classification of Diseases, Ninth Revision, Clinical Modification* codes, 290.xx–311.xx; *International Classification of Diseases, Tenth Revision, Clinical Modification* codes, F01.xx–F99.xx) and costs of mental health–related treatments.
†Included in the initial model but excluded due to insignificancy (*P* ≥ 0.05).
‡Bipolar disorder, depression, anxiety, personality disorder, or substance abuse disorders.
§Mood stabilizers, antidepressants, antianxiety medications, sedatives, or hypnotics.
‖Antidiabetic, lipid-lowering, or antihypertensive medications.

in all-cause medical cost, in which, additionally, the large variance of all-cause medical costs made it harder to identify differences between the impacts of the OAAs on medical costs.

Previous research supports the idea that medication choice can affect costs. Using MarketScan data, Lin et al[27] reported decreases in SCZ-related hospital costs associated with long-acting injectable antipsychotic agents compared with oral antipsychotic agents. Using PharMetrics data, Joyce et al[20] found decreases in overall and inpatient costs with different atypical antipsychotic agents. However, neither study included brexpiprazole. Aigbogun et al[5] used clinical trial data from patients with SCZ initiating brexpiprazole treatment to develop an economic model to assess the cost-effectiveness of brexpiprazole versus other branded therapies, and they found that brexpiprazole may lead to clinical benefits and medical cost savings. Although the current study focused on the comparisons among different OAAs, previous literature has examined cost differences between long-acting injectable therapies and OAAs.[27–31]

This retrospective study adds to the current information regarding the potential benefits of brexpiprazole in SCZ treatment, which has thus far been based on clinical trial data and has not included comparisons of as many antipsychotic agents. In addition, clinical trials are often conducted within a restricted study population. Our study included a more generalizable sample of patients with a variety of insurance types.

This study had several limitations. First, there were limitations related to the data source because insurance claims are designed for reimbursement; misclassification and coding errors are possible. Clinical information, such as disease severity or reasoning behind choice of drug therapy, is not directly available. In addition, due to the years of data available and brexpiprazole's approval date, a future study with a larger sample size of brexpiprazole users and other more recently approved treatments is warranted. Second, our study's objective was to directly compare individual OAAs; therefore, patients treated with multiple antipsychotic agents were not included, even though polypharmacy is common in SCZ.[4] Third, brexpiprazole users had the highest proportion of nonindex antipsychotic medication use. A potential

Table V. Adjusted estimates of health care costs.

Parameter	Linear Regression Models				Linear Regression Models			
	Total All-cause Costs		Total Psychiatric* Costs		All-cause Medical Costs[†]		Psychiatric* Costs[†]	
	Estimate (95% CI)	P	Estimate (95% CI)	P	Estimate (95% CI)	P	Estimate (95% CI)	P
Age group, y								
18–30 vs ≥65	$17,199 (11,352 to 23,046)	<0.001	$11,092 (7340–14,845)	<0.001	$12,390 (6704–18,076)	<0.001	$10,597 (7440–13,754)	<0.001
31–64 vs ≥65	$13,801 (8895–18,707)	<0.001	$6575 (3413–9736)	<0.001	$8803 (4034–13,572)	<0.001	$6476 (3760–9191)	<0.001
Female vs male	—	NS[‡]	$–1701 (–3393 to –8)	0.049	—	NS[‡]	—	NS[‡]
Insurance type								
Medicaid vs commercial	—	NS[‡]	$4253 (2049–6457)	<0.001	—	NS[‡]	—	NS[‡]
Medicare vs commercial	—	NS[‡]	$827 (–2108 to 3762)	0.581	—	NS[‡]	—	NS[‡]
Charlson Comorbidity Index score	$6260 (5527–6994)	<0.001	—	NS[‡]	$5154 (4441–5866)	<0.001	$525 (127–923)	0.010
Any psychiatric comorbidities[§] (Y vs N)	—	NS[‡]	—	NS[‡]	—	NS[‡]	$2303 (120–4486)	0.039
Hyperlipidemia (Y vs N)	$4618 (1166–8070)	0.009	$4719 (2843–6596)	<0.001	$4266 (911–7620)	0.013	$3327 (1480–5173)	<0.001
Hypertension (Y vs N)	$6487 (3013–9960)	<0.001	—	NS[‡]	$5149 (1780–8519)	0.003	—	NS[‡]
Any baseline ED visits (Y vs N)	$3566 (534–6598)	0.021	—	NS[‡]	$3645 (696–6595)	0.015	$2324 (628–4021)	0.007
Any baseline inpatient hospitalization (Y vs N)	$14,903 (11,883 to 17,922)	<0.001	$12,687 (10,995 to 14,378)	<0.001	$15,799 (12,864 to 18,734)	<0.001	$11,180 (9456–12,904)	<0.001
Baseline nonindex antipsychotic medications (Y vs N)	$6905 (3533–10,278)	<0.001	$10,664 (8709–12,618)	<0.001	$3869 (590–7147)	0.021	$8292 (6515–10,069)	<0.001
Baseline psychiatric medication‖ use (Y vs N)	$6574 (3009–10,140)	<0.001	$3136 (1097–5174)	0.003	$5401 (1937–8866)	0.002	—	NS[‡]

Table V. (*Continued*)

Parameter	Linear Regression Models				Linear Regression Models			
	Total All-cause Costs		Total Psychiatric* Costs		All-cause Medical Costs†		Psychiatric* Costs†	
	Estimate (95% CI)	P	Estimate (95% CI)	P	Estimate (95% CI)	P	Estimate (95% CI)	P
Baseline nonpsychiatric medication¶ use (Y vs N)	—	NS‡	—	NS‡	—	NS‡	—	NS‡
PDC of index medication (range, 0–1)	—	NS‡	—	NS‡	$-5290 (–9245 to –1335)	0.009	$−3311 (−5566 to −1056)	0.004
	Estimate (Bootstrap# 95% CI)	P	Estimate (Bootstrap# 95% CI)	P	Estimate (Bootstrap# 95% CI)	P	Estimate (Bootstrap# 95% CI)	P
Index treatment								
Aripiprazole vs brexpiprazole	$956 (–8083 to 9995)	0.836	$−2238 (–7605 to 3129)	0.414	$5244 (–3250 to 13,738)	0.226	$1894 (–3067 to 6855)	0.454
Lurasidone vs brexpiprazole	$2547 (–6023 to 11,117)	0.560	$2269 (–3255 to 7793)	0.421	$3391 (–4740 to 11,522)	0.414	$3507 (–1621 to 8636)	0.180
Olanzapine vs brexpiprazole	$−2701 (–10,540 to 5138)	0.500	$−1358 (–6834 to 4117)	0.627	$5511 (–1741 to 12,763)	0.136	$6744 (1694–11,795)	0.009
Paliperidone vs brexpiprazole	$7203 (–964 to 15,370)	0.084	$8215 (2402–14,027)	0.006	$5663 (–1793 to 13,120)	0.137	$7330 (2002–12,657)	0.007
Quetiapine vs brexpiprazole	$−3324 (–11,264 to 4617)	0.412	$−4957 (–10,249 to 334)	0.066	$5307 (–2123 to 12,736)	0.162	$3306 (–1542 to 8155)	0.181
Risperidone vs brexpiprazole	$−3864 (–11,572 to 3844)	0.326	$−4175 (–9387 to 1037)	0.116	$4044 (–3114 to 11,203)	0.268	$3643 (–1161 to 8447)	0.137
Ziprasidone vs brexpiprazole	$−535 (–9293 to 8222)	0.905	$−2810 (–8617 to 2998)	0.343	$8258 (–37 to 16,554)	0.051	$5669 (348–10,989)	0.037
	Adjusted Mean (Bootstrap# 95% CI) Total All-cause Costs		Adjusted Mean (Bootstrap# 95% CI) Total Psychiatric* Costs		Adjusted Mean (Bootstrap# 95% CI) All-Cause Medical Costs†		Adjusted Mean (Bootstrap# 95% CI) Psychiatric* Costs†	
Index treatment								
Aripiprazole	$41,220 (35,656 to 46,784)		$21,613 (19,543 to 23,683)		$30,686 (25,344 to 36,029)		$13,908 (11,936 to 15,880)	
Lurasidone	$42,811 (37,769 to 47,854)		$26,120 (23,608 to 28,632)		$28,833 (23,839 to 33,827)		$15,521 (13,114 to 17,927)	
Olanzapine	$37,564 (34,626 to 40,502)		$22,493 (20,349 to 24,636)		$30,953 (28,116 to 33,790)		$18,758 (16,689 to 20,826)	
Paliperidone	$47,468 (43,043 to 51,892)		$32,066 (28,779 to 35,353)		$31,105 (27,018 to 35,193)		$19,343 (16,294 to 22,392)	

Table V. (Continued)

	Adjusted Mean (Bootstrap[#] 95% CI) Total All-cause Costs	Adjusted Mean (Bootstrap* 95% CI) Total Psychiatric* Costs	Adjusted Mean (Bootstrap[#] 95% CI) All-Cause Medical Costs[†]	Adjusted Mean (Bootstrap[#] 95% CI) Psychiatric* Costs[†]
Quetiapine	$36,941 (33,590 to 40,292)	$18,894 (17,036 to 20,751)	$30,749 (27,485 to 34,012)	$15,319 (13,569 to 17,070)
Risperidone	$36,401 (33,735 to 39,066)	$19,676 (18,058 to 21,294)	$29,486 (26,905 to 32,068)	$15,656 (14,096 to 17,217)
Ziprasidone	$39,729 (33,964 to 45,494)	$21,042 (17,831 to 24,253)	$33,701 (27,994 to 39,407)	$17,682 (14,624 to 20,740)
Brexpiprazole	$40,264 (33,116 to 47,413)	$23,851 (18,907 to 28,795)	$25,442 (18,828 to 32,056)	$12,013 (7488–16,538)

ED = emergency department; N = no; NS = not significant; PDC = proportion of days covered; Y = yes.
*Claims with a primary diagnosis of any mental disorder (International Classification of Diseases, Ninth Revision, Clinical Modification codes, 290.xx–311.xx; International Classification of Diseases, Tenth Revision, Clinical Modification codes, F01.xx–F99.xx) and costs of mental health–related treatments.
[†]Total inpatient and outpatient service costs; excludes outpatient pharmacy costs.
[‡]Included in the initial model but excluded due to insignificancy (P ≥ 0.05).
[§]Bipolar disorder, depression, anxiety, personality disorder, or substance abuse disorders.
[||]Mood stabilizers, antidepressants, antianxiety medications, sedatives, or hypnotics.
[¶]Antidiabetic, lipid-lowering, or antihypertensive medications.
[#]A total of 1000 bootstrap samples were used.

explanation for this finding could be that the cohort of brexpiprazole users consisted of fewer patients with new diagnoses of SCZ. Because brexpiprazole is a newer drug, these patients may have cycled through multiple medications before starting brexpiprazole. It is possible that the lack of statistically significant health care utilization results indicates an inability to control for disease severity. Fourth, data limitations also did not allow us to account for why only the differences in hospitalization rates between brexpiprazole and paliperidone were statistically significant. One hypothesis could be that paliperidone was associated with higher rates of adverse effects; however, in a meta-analysis comparing the efficacy and tolerability of 15 antipsychotic drugs, Leucht et al[32] found that prolactin increase was the only side effect that paliperidone was more significantly associated with versus the other antipsychotic agents; brexpiprazole was not included in this analysis.

CONCLUSIONS
In patients with SCZ, use of brexpiprazole was associated with a lower number of psychiatric hospitalizations and lower psychiatric costs compared with paliperidone. Differences in the number of all-cause hospitalizations and medical costs between treatments were not statistically significant. Although treatment decisions are driven by a number of factors (eg, clinical circumstances and drug costs), choice of OAA may affect different components of health care costs in patients with SCZ.

DISCLOSURES

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design, and implementation of the study; to the interpretation of the results; and to the writing of the manuscript. Dr. Chang performed the statistical analyses for the study.

REFERENCES

1. The National Institute of Mental Health. Schizophrenia. Health & Education − Statistics. https://www.nimh.nih.gov/health/statistics/prevalence/schizophrenia.shtml. Published November 2017. Accessed November 21, 2018.

2. Cloutier M, Aigbogun MS, Guerin A, et al. The economic burden of schizophrenia in the United States in 2013. *J Clin Psychiatr*. 2016;77:764−771. https://doi.org/10.4088/JCP.15m10278.

3. Ascher-Svanum H, Zhu B, Faries DE, et al. The cost of relapse and the predictors of relapse in the treatment of schizophrenia. *BMC Psychiatry*. 2010;10:2. https://doi.org/10.1186/1471-244X-10-2.

4. Lehman AF, Lieberman JA, Dixon LB, et al. Practice guideline for the treatment of patients with schizophrenia, second edition. *Am J Psychiatr*. 2004;161(2 Suppl):1−56.

5. Aigbogun MS, Liu S, Kamat SA, Sapin C, Duhig AM, Citrome L. Relapse prevention: a cost-effectiveness analysis of brexpiprazole treatment in adult patients with schizophrenia in the USA. *Clin Outcomes Res*. 2018;10:443−456. https://doi.org/10.2147/CEOR.S160252.

6. Berger A, Edelsberg J, Sanders KN, Alvir JMJ, Mychaskiw MA, Oster G. Medication adherence and utilization in patients with schizophrenia or bipolar disorder receiving aripiprazole, quetiapine, or ziprasidone at hospital discharge: a retrospective cohort study. *BMC Psychiatry*. 2012;12:99. https://doi.org/10.1186/1471-244X-12-99.

7. de Castro APW, Elkis H. Rehospitalization rates of patients with schizophrenia discharged on haloperidol, risperidone or clozapine. *Braz J Psychiatry*. 2007;29(3):207−212.

8. Yan T, Greene M, Chang E, Hartry A, Touya M, Broder MS. Medication adherence and discontinuation of aripiprazole once-monthly 400 mg (AOM 400) versus oral antipsychotics in patients with schizophrenia or bipolar I disorder: a real-world study using US claims data. *Adv Ther*. 2018;35:1612−1625. https://doi.org/10.1007/s12325-018-0785-y.

9. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373−383.

10. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992;45:613−619.

11. Agency for Healthcare Research and Quality. *HCUP chronic condition indicator. Healthcare cost and utilization Project (HCUP)*; June 2015. www.hcup-us.ahrq.gov/toolssoftware/chronic/chronic.jsp.

12. Gilmer TP, Dolder CR, Lacro JP, et al. Adherence to treatment with antipsychotic medication and health care costs among Medicaid beneficiaries with schizophrenia. *Am J Psychiatr*. 2004;161:692−699. https://doi.org/10.1176/appi.ajp.161.4.692.

13. Ascher-Svanum H, Faries DE, Zhu B, Ernst FR, Swartz MS, Swanson JW. Medication adherence and long-term functional outcomes in the treatment of schizophrenia in usual care. *J Clin Psychiatr*. 2006;67:453−460.

14. Ascher-Svanum H, Zhu B, Faries DE, Furiak NM, Montgomery W. Medication adherence levels and differential use of mental-health services in the treatment of schizophrenia. *BMC Res Notes*. 2009;2:6. https://doi.org/10.1186/1756-0500-2-6.

15. Higashi K, Medic G, Littlewood KJ, Diez T, Granström O, De Hert M. Medication adherence in schizophrenia: factors influencing adherence and consequences of nonadherence, a systematic literature review. *Ther Adv Psychopharmacol*. 2013;3:200−218. https://doi.org/10.1177/2045125312474019.

16. Lang K, Meyers JL, Korn JR, et al. Medication adherence and hospitalization among patients with schizophrenia treated with antipsychotics. *Psychiatr Serv Wash DC*. 2010;61:1239−1247. https://doi.org/10.1176/appi.ps.61.12.1239.

17. Weiden PJ, Kozma C, Grogg A, Locklear J. Partial compliance and risk of rehospitalization among California Medicaid patients with schizophrenia. *Psychiatr Serv Wash DC*. 2004;55:886−891. https://doi.org/10.1176/appi.ps.55.8.886.

18. Nau D. *Proportion of Days Covered (PDC) as a Preferred Method of Measuring Medication Adherence*. Springfield, VA: Pharmacy Quality Alliance; 2012. http://www.pqaalliance.org/files/PDCvsMPRfinal.pdf. Accessed November 21, 2018.

19. Ascher-Svanum H, Zhu B, Faries D, Landbloom R, Swartz M, Swanson J. Time to discontinuation of atypical versus typical antipsychotics in the naturalistic treatment of schizophrenia. *BMC Psychiatry*. 2006;6. https://doi.org/10.1186/1471-244X-6-8.

20. Joyce AT, Harrison DJ, Loebel AD, Ollendorf DA. Impact of atypical antipsychotics on outcomes of care in schizophrenia. *Am J Manag Care*. 2005;11(8 Suppl):S254−S261.

21. Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet*. 2009;373:31−41.

22. Eaves S, Rey JA. Brexpiprazole (Rexulti): a new monotherapy for schizophrenia and adjunctive therapy for major depressive disorder. *P T Peer-rev J Formul Manag.* 2016;41:418—422.

23. Das S, Barnwal P, Winston AB, Mondal S, Saha I. Brexpiprazole: so far so good. *Ther Adv Psychopharmacol.* 2016;6:39—54. https://doi.org/10.1177/2045125315614739.

24. Diefenderfer LA, Iuppa C. Brexpiprazole: a review of a new treatment option for schizophrenia and major depressive disorder. *Ment Health Clin.* 2017;7:207—212. https://doi.org/10.9740/mhc.2017.09.207.

25. Bruijnzeel D, Tandon R. Spotlight on brexpiprazole and its potential in the treatment of schizophrenia and as adjunctive therapy for the treatment of major depression. *Drug Des Devel Ther.* 2016;10:1641—1647. https://doi.org/10.2147/DDDT.S85089.

26. Citrome L, Ota A, Nagamizu K, Perry P, Weiller E, Baker RA. The effect of brexpiprazole (OPC-34712) and aripiprazole in adult patients with acute schizophrenia: results from a randomized, exploratory study. *Int Clin Psychopharmacol.* 2016;31:192—201. https://doi.org/10.1097/YIC.0000000000000123.

27. Lin J, Wong B, Offord S, Mirski D. Healthcare cost reductions associated with the use of LAI formulations of antipsychotic medications versus oral among patients with schizophrenia. *J Behav Health Serv Res.* 2013;40:355—366. https://doi.org/10.1007/s11414-013-9329-z.

28. Shah A, Xie L, Kariburyo F, Zhang Q, Gore M. Treatment patterns, healthcare resource utilization and costs among schizophrenia patients treated with long-acting injectable versus oral antipsychotics. *Adv Ther.* 2018;35:1994—2014. https://doi.org/10.1007/s12325-018-0786-x.

29. Pilon D, Tandon N, Lafeuille MH, et al. Treatment patterns, health care resource utilization, and spending in Medicaid beneficiaries initiating second-generation long-acting injectable agents versus oral atypical antipsychotics. *Clin Ther.* 2017;39:1972—1985. https://doi.org/10.1016/j.clinthera.2017.08.008. e2.

30. Kamat S, Offord S, Docherty J, et al. Reduction in inpatient resource utilization and costs associated with long-acting injectable antipsychotics across different age groups of Medicaid-insured schizophrenia patients. *Drugs Context.* 2015;4:1—12. https://doi.org/10.7573/dic.212267.

31. Baser O, Xie L, Pesa J, Durkin M. Healthcare utilization and costs of Veterans Health Administration patients with schizophrenia treated with paliperidone palmitate long-acting injection or oral atypical antipsychotics. *J Med Econ.* 2015;18:357—365. https://doi.org/10.3111/13696998.2014.1001514.

32. Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet.* 2013;382:951—962. https://doi.org/10.1016/S0140-6736(13)60733-3.

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