Original Research

Health Care Resource Use, Costs, and Diagnosis Patterns in Patients With Schizophrenia and Bipolar Disorder: Real-world Evidence From US Claims Databases

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ABSTRACT

Purpose: Schizophrenia (SCZ) and bipolar disorder (BD) are typically viewed as nonconcurrent psychiatric disorders, yet patients may experience mood and SCZ symptoms simultaneously. Several studies have shown overlap between SCZ and BD symptoms and susceptibility genes. This study explored the following: (1) patterns of administrative claims; (2) demographic characteristics and comorbidities; (3) health care resource use; and (4) health care costs in patients with diagnoses of SCZ, type I BD (BD-I), and both in a real-world setting.

Methods: This study was a retrospective cohort trial using 4.5 years (January 1, 2012–June 30, 2016) of Truven MarketScan commercial, Medicaid, and Medicare supplemental databases. We considered a patient to have a new episode of SCZ if he or she had 1 inpatient claim or 2 outpatient claims for SCZ within the identification period (January 1, 2013–June 30, 2015). BD-I was defined in an analogous way. Three study cohorts were defined: (1) SCZ alone (cohort I), met the claims-based diagnostic criteria for SCZ; (2) BD-I alone (cohort II), met the claims-based diagnostic criteria for BD-I; and (3) BD-I and SCZ (cohort III), met the claims-based diagnostic criteria for both SCZ and BD-I.

Findings: Of the 63,725 patients in the final sample, 11.5% (n = 7336) had a new episode of SCZ alone (cohort I), 80.8% (n = 51,480) had a new episode of BD-I alone (cohort II), and 7.7% (n = 4909) had new episodes of both SCZ and BD-I (cohort III). Considering cohort III, 18.8% (n = 927) received both diagnoses on the same day. In the year after diagnosis, the cohort having a diagnosis of both SCZ and BD-I (cohort III) had the highest all-cause hospitalization rates (67.4% vs 39.5% in SCZ alone and 33.7% in BD-I alone) and the highest mean (SD) number of emergency department visits (3.44 [7.1] vs 1.39 [3.5] in SCZ alone and 1.29 [3.2] in BD-I alone). All-cause total health care costs were highest in the cohort having a diagnosis of both SCZ and BD-I (mean [SD]), $51,085 [$62,759]), followed by the SCZ alone cohort ($34,204 [$52,995]), and the BD-I alone cohort ($26,396 [$48,294]).

Implications: Our analyses indicate that a substantial number of patients received diagnoses of both SCZ and BD-I, based on claims, in a 2.5-year period. Patients with a diagnosis of both SCZ and BD-I had higher health care utilization and costs than patients with either diagnosis alone. We identified differential patient characteristics, utilization of medications and health care services, and health care costs among the cohorts. (*Clin Ther*. 2018;40:1670–1682)

Key words: schizophrenia, bipolar disorder, diagnosis patterns, healthcare resource utilization and costs, administrative claims data.

This study was presented at the 6th Biennial Schizophrenia International Research Society Conference, April 4–8, 2018, Florence, Italy, and cited elsewhere (Greene M, Yan T, Chang E, et al. Schizophrenia and bipolar disorder diagnosis patterns: real-world evidence from US claims databases. *Schizophrenia Bulletin*. 2018;44:S97–S98).

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INTRODUCTION

Schizophrenia and bipolar disorder (BD) are severe, relapsing psychiatric disorders affecting ~0.3% (~0.76 million) and 2.8% (~7.1 million) adults in the United States, respectively.[1,2] Schizophrenia is characterized by hallucinations, lack of emotional response, and bizarre or paranoid delusions; BD is characterized by episodes of mania, hypomania, and major depression.

Both schizophrenia and BD are costly conditions associated with significant health care resource use. The nationwide annual direct and indirect costs associated with schizophrenia and BD were recently estimated to be more than $155 billion and $200 billion, respectively.[3,4] A recent claims-based analysis reported average overall costs among people with schizophrenia of $22,338.[5] A different study using claims data estimated direct costs of type I BD (BD-I) to be $18,759 per patient.[3] Patients with BD use 3 to 4 times more health care resources than patients without BD,[6] and the majority of patients with BD have at least 1 psychiatric hospitalization in their lifetime.[7] In a recent study of patients with schizophrenia and BD-I who initiated long-acting injectable antipsychotic agents, 66.5% of patients with schizophrenia and 81.4% of patients with BD-I had at least 1 inpatient hospitalization or emergency department visit during the year before initiation of long-acting injectable antipsychotic agents.[8]

Despite the fact that schizophrenia and BD have long been viewed as 2 distinct psychiatric disorders, and are currently classified separately according to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) and *International Classification of Diseases* (ICD) guidelines, diagnostic confusion may occur when patients with BD experience schizophrenia-like hallucinations and delusions during an episode of psychotic mania or psychotic depression. The coexistence of schizophrenia-like and BD symptoms tends to occur more frequently in the early stages of the disease, and this scenario can lead to misdiagnosis.[9–11] A variety of clinicians and researchers have questioned the validity of the categorical approach to these diseases, as psychotic symptoms can be present in both diseases, suggesting that they are less distinct than the DSM and ICD indicate.[9,12] In fact, several recent studies have shown that the majority of real-world patients have multiple psychiatric disorders,[13,14] and rates of mental health multimorbidity tend to be higher in patients with schizophrenia and BD compared with other psychiatric patients.[15,16] Psychiatric multimorbidity, and its associated clinical complexity, is increasingly recognized as ubiquitous by mental health professionals and according to research.[13]

Several theories provide potential explanations for the overlap between schizophrenia and BD symptoms. For example, the physiological model, which has been confirmed by modern molecular studies, suggests shared susceptibility genes exist in the 2 diseases.[17,18] Also, schizophrenia and BD share similar risk factors: recent stress, childbirth, perinatal complications, and a family history of psychiatric disorders are risk factors for both disorders.[19] Another theory, the continuum model, poses that all major psychiatric disorders are interconnected by a continuum ranging from unipolar disorder, to BD, to schizoaffective disorder, to schizophrenia, with increasing severity across the continuum.[20]

Insurance claims are often used to examine prescribing patterns, cost, and even quality of care. It is clear from claims-based analyses that patients receive claims for both schizophrenia and BD despite the clinical view that these are 2 separate disorders. Based on a search of the literature using PubMed, there are no studies that have examined diagnosis and treatment utilization patterns in patients with claims for both schizophrenia and BD. Therefore, the aim of the present study was to examine diagnosis patterns based on claims in a real-world setting among patients with new episodes of schizophrenia alone, type I BD (BD-I) alone, and both schizophrenia and BD-I. We described demographic characteristics, comorbidities, health care resource utilization, and health care costs in these groups of patients as a way to examine different diagnosis patterns.

MATERIALS AND METHODS

Data Sources

Data from the Truven MarketScan Medicaid, commercial, and Medicare supplemental databases (Truven Health Analytics, Ann Arbor, Michigan) from January 1, 2012, to June 30, 2016, were used to examine the diagnosis patterns, health care resource use, and costs of patients with both schizophrenia and BD-I diagnoses. The MarketScan Medicaid, commercial, and Medicare supplemental databases are Health Insurance Portability and Accountability Act–compliant administrative claims databases.

The Medicaid database contains the pooled health care experience of ~40 million Medicaid enrollees

from multiple states. It includes inpatient and outpatient services and outpatient prescription drug claims, as well as information on enrollment, long-term care, and other medical care. In addition to standard demographic variables such as age and sex, the database includes variables of particular value to researchers investigating Medicaid populations (eg, ethnicity, maintenance assistance status, Medicare eligibility).

The commercial data included medical encounters from ~65 million individuals and their dependents insured by employer-sponsored plans (ie, non-Medicare eligible). Coverage was provided under a variety of fee-for-service, fully capitated, and partially capitated health plans, including preferred provider organizations, point of service plans, indemnity plans, and health maintenance organizations.

The Medicare supplemental data included ~5.3 million Medicare-eligible retired employees and their spouses with employer-sponsored Medicare supplemental plans. Given the de-identified nature of the data used in the present study, informed consent was not required according to the Health Insurance Portability and Accountability Act rules.

Study Population and Measures

Three cohorts were identified in this study: (1) patients with new episodes of schizophrenia alone (cohort I); (2) patients with new episodes of BD-I alone (cohort II); and (3) patients with new episodes of both schizophrenia and BD-I (cohort III). Figure 1 presents study timelines for all 3 cohorts. Patients were deemed to have a diagnosis of schizophrenia or BD-I if they had at least 1 inpatient claim or at least 2 outpatient claims (on separate dates) for schizophrenia disorders (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] codes: 295.xx, excluding 295.4x and 295.7x; or *International Classification of Diseases, Tenth Revision, Clinical Modifications* [ICD-10-CM], codes: F20x, excluding F20.81x) or for BD-I (ICD-9-CM codes: 296.0x, 296.1x, 296.4x, 296.5x, 296.6x, 296.7x, 296.8x, excluding 296.82; ICD-10-CM codes: F30.x, F31.x, excluding F31.81). We therefore use the term "diagnosis" to denote that a patient met the claims-based criteria for a disease of interest (ie, he or she received at least 1 inpatient claim or at least 2 outpatient claims for that disease).

To ensure that we were examining new episodes of care, in cohort I, patients were excluded if they had any medical claims for schizophrenia in the 1-year period before their first schizophrenia diagnosis date found in the study identification period between January 1, 2013, and June 30, 2015. Similarly, in cohort II, patients were excluded if they had any medical claims for BD-I in the 1-year period before their first BD-I diagnosis date found in the study identification period. However, patients with any medical claims for BD-I in the 1-year period before their first schizophrenia diagnosis date found in the study identification period were included in cohort III (patients with new episodes of both schizophrenia and BD-I).

We required patients in all cohorts to be aged ≥18 years on the index date and have continuous health plan enrollment for ≥1 year before (baseline) and after (follow-up) the index date. Due to incomplete data, in the Medicaid database, we further excluded patients who had Medicare and Medicaid dual eligibility; had capitated insurance plans; lacked pharmacy coverage; or lacked mental health coverage during the entire study period.

Patient characteristics examined included demographic variables (eg, age, sex, geographic region, race); insurance type; Charlson Comorbidity Index[21]; number of chronic condition indicators[22]; other comorbidities of interest; medication use (baseline and 1-year postindex); health care utilization 1-year postindex, including all-cause and psychiatric office visits, inpatient hospitalizations, and emergency department visits; and costs in the 1-year postindex period, including all-cause and psychiatric total, inpatient, outpatient, and pharmacy. Health care costs were adjusted to 2016 US dollars.

In an exploratory analysis examining diagnosis patterns in patients with both schizophrenia and BD-I (cohort III) based on claims, we further divided patients with new episodes of both into 2 groups: (1) those who met BD-I criteria only in the year before meeting the schizophrenia criteria, with the first diagnosis date of schizophrenia as the index date; (2) those who met schizophrenia criteria only in the year before, or on the same day as, meeting BD-I criteria, with the first diagnosis date of BD-I as the index date; and (3) those who met BD-I criteria both in the year before and the year after meeting the schizophrenia criteria, with the first diagnosis date of schizophrenia as the index date.

Patients with schizoaffective disorder have prominent mood components (eg, manic episodes or depression) along with psychosis, but psychosis and mood symptoms often occur at different times.[23] Because

these patients differ clinically from those with BD-I and schizophrenia, as a sensitivity analysis to ensure the results were not driven by patients who truly had schizoaffective disorder, we excluded those with additional diagnostic claims for schizoaffective disorder and examined patient characteristics, health care utilization, and costs in patients without a diagnosis of schizoaffective disorder based on claims. Patients were deemed to have a diagnosis of schizoaffective disorder if they had at least 1 inpatient or 2 outpatient claims with a schizoaffective disorder diagnosis (ICD-9-CM code 295.7x or ICD-10-CM code F25.x) in any diagnosis field during the baseline or follow-up period.

Statistical Analysis

Descriptive statistics, including means, SDs, and relative frequencies and percentages for continuous and categorical data, respectively, were reported for all cohorts. In addition, for group comparisons, χ^2 tests for categorical variables, t tests for normally distributed continuous variables, and Kruskal-Wallis tests for nonnormally distributed variables were performed. This study aimed to provide a descriptive comparison of the 3 cohorts of patients, not to attempt to make the groups similar with regard to clinical characteristics by using statistical models. However, as an exploratory analysis, to determine if results were primarily due to differences in insurance type, we controlled for age group, sex, and insurance type by using regression models. Logistic regression and linear regression models were performed for dichotomous and continuous outcomes. A sensitivity analysis was performed with patients stratified according to schizoaffective disorder status. All data transformations and statistical analyses were performed by using SAS version 9.4 (SAS Institute, Inc, Cary, North Carolina).

RESULTS

Of the 63,725 patients in the final sample, 11.5% (n = 7336) had a new episode of schizophrenia alone (cohort I), 80.8% (n = 51,480) had a new episode of BD-I alone (cohort II), and 7.7% (n = 4909) had new episodes of both schizophrenia and BD-I (cohort III). Patients with different diagnoses and different patterns of diagnosis significantly differed in age, sex, geographic region, race, and insurance type ($P < 0.001$) (Table I). Patients with schizophrenia alone (cohort I) were older than patients in the other 2 cohorts (mean age of 46.6 years vs a range of 41.6−41.8 years). More than one half of patients in cohorts II and III were female, whereas 46.1% of patients with schizophrenia alone (cohort I) were female. More African-American patients than white patients were diagnosed with schizophrenia alone (cohort I) (37% vs 18%), whereas more white patients than African-American patients were diagnosed with BD-I alone (cohort II) (14.4% vs 5.9%). The majority (>64%) of patients in all cohorts, except those with a diagnosis of BD-I alone (cohort II), had Medicaid; the majority (68.3%) of patients with BD-I alone (cohort II) had commercial insurance.

Comorbidities were statistically significantly different ($P < 0.001$) among patients with different diagnoses and different patterns of diagnosis (Table II). Patients with claims for both diagnoses (cohort III) had more chronic conditions, with a mean (SD) of 4.1 (2.5), compared with 3.1 (2.5) in patients with schizophrenia alone (cohort I) and 3.2 (2.3) in patients with BD-I alone (cohort II); they also had more substance abuse disorders (33.7%) compared with patients with schizophrenia alone (cohort I; 13.1%) and patients with BD-I alone (cohort II; 14.7%).

Medication use at baseline and 1-year postindex (Table III) was statistically significantly different among patients with different diagnoses and different diagnosis patterns ($P < 0.001$). In the baseline period, patients in cohort III had higher rates of atypical and typical antipsychotic use, with a mean of 76.2%, compared with patients with schizophrenia alone (cohort I) and BD-I alone (cohort II), whose rates were 56% and 32%, respectively. All measured medication use (typical and atypical antipsychotic agents, psychiatric medications, and somatic medications) increased from baseline to 1-year postindex in all groups.

In the year after diagnosis, all-cause and psychiatric health care utilizations were statistically significantly different ($P < 0.001$) between cohorts (Figure 2). The all-cause hospitalization rate in cohort III was 67.4%, compared with 39.5% in cohort I and 33.7% in cohort II, respectively. The mean (SD) of all-cause emergency department visits in cohort III was 3.44 (7.1) times per year, compared with 1.39 (3.5) in cohort I and 1.29 (3.2) in cohort II. Psychiatric inpatient hospitalizations were highest among the cohort with both diagnoses (cohort III), with a mean (SD) of 1.1 (1.8) per year versus 0.3 (0.8) in both the BD alone (cohort II) and

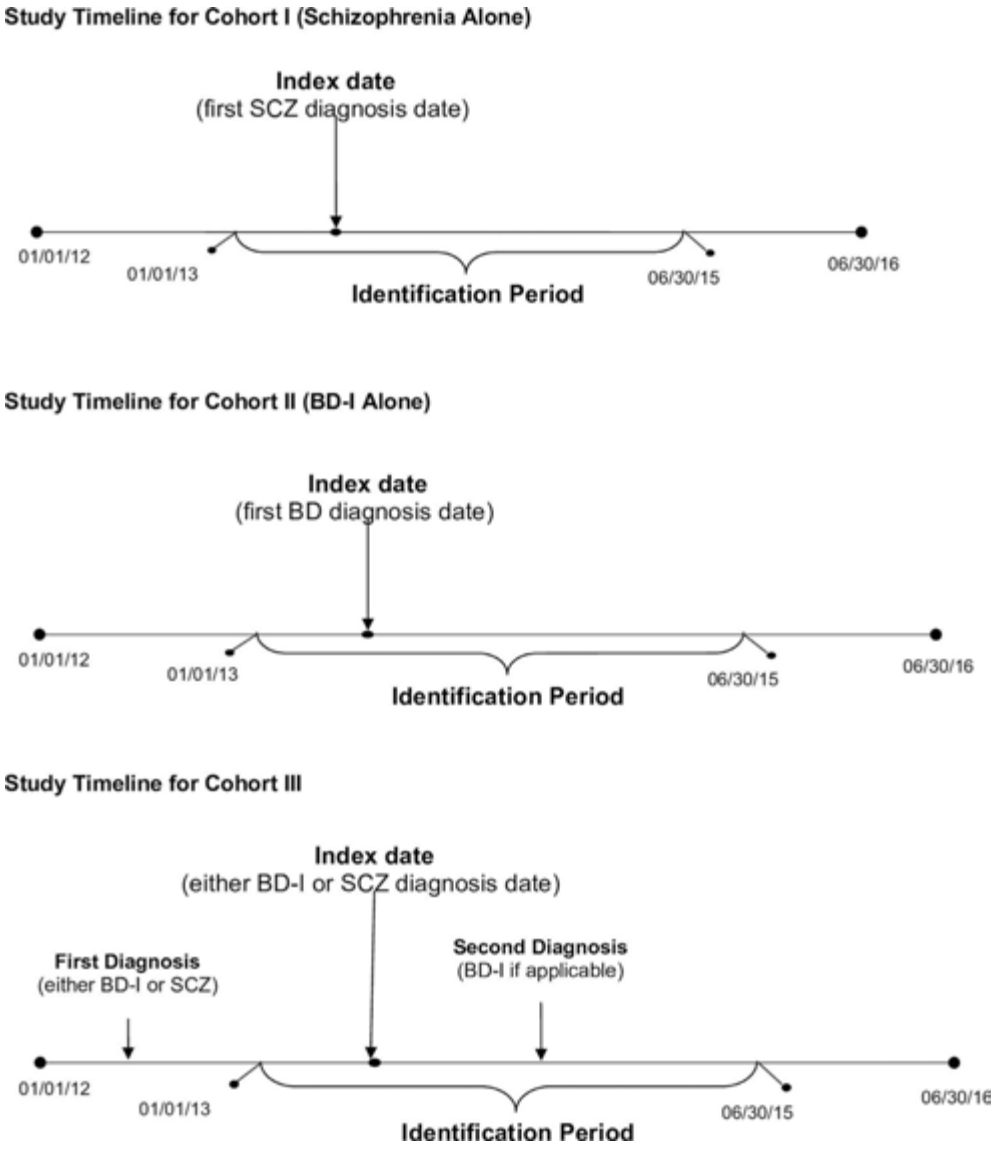

Figure 1. Study timelines for cohorts I (schizophrenia [SCZ] alone), cohort II (type I bipolar disorder [BD-I] alone), and cohort III (both SCZ and BD-I).

schizophrenia alone (cohort I) cohorts. Psychiatric emergency department visit rates per year were highest among the cohort with claims for both diagnoses (cohort III), with a mean (SD) of 0.7 (1.8) versus 0.2 (0.8) and 0.3 (1.6) in the BD alone (cohort II) and schizophrenia alone (cohort I) cohorts. Results from risk-adjusted models were consistent with the unadjusted results. Patients with both claims-based diagnoses (ie, schizophrenia and BD-I) had significantly increased adjusted rates of any inpatient hospitalization and psychiatric inpatient hospitalization compared with patients with schizophrenia alone and BD-I alone in the 1-year follow-up period (all $P < 0.001$). Specifically, 67.3% (95% CI, 66.0–68.7) and 55.1% (95% CI, 53.7–56.6) of patients with both claims-based diagnoses had at least 1 all-cause hospitalization and at least 1 psychiatric hospitalization, respectively; 37.9% (95% CI, 36.7–39.0) and 26.3% (95% CI, 25.3–27.5) of schizophrenia alone patients had at least 1 all-cause hospitalization and at least 1 psychiatric hospitalization; and 33.7% (95% CI, 33.3–34.1) and 19.7% (95% CI,

19.3−20.0) of BD-I alone patients had at least 1 all-cause hospitalization and at least 1 psychiatric hospitalization in the 1-year follow-up period.

All-cause and psychiatric health care costs were statistically significantly different ($P < 0.001$) among patients with different diagnoses and different patterns of diagnosis in the 1-year postindex period (Figure 3). All-cause costs were highest among cohort III, with a mean (SD) of $51,085 (62,759) versus $26,396 (48,924) and $34,204 (52,995) in the BD alone (cohort II) and schizophrenia alone (cohort I) patients, respectively. Psychiatric health care costs were highest among cohort III, with a mean of $25,098 (36,750) versus $9449 (20,748) and $12,722 (22,239) in the BD alone (cohort II) and schizophrenia alone (cohort I) patients. Results from risk-adjusted models were consistent with the unadjusted results. Patients with both diagnoses based on claims had significantly increased adjusted all-cause and psychiatric costs compared with patients with schizophrenia alone and BD-I alone in the 1-year follow-up period (all $P < 0.001$). Mean all-cause and psychiatric costs for patients with both diagnoses were $48,451 (95% CI, 47,026−49,876) and $25,696 (95% CI, 25,049−26,342); mean all-cause and

Table I. Patient demographic characteristics.

Characteristic	Cohort I: SCZ alone	Cohort II: BD-I alone	Cohort III: Both SCZ and BD-I	P*,†
No. (%) of patients	7336 (11.5)	51,480 (80.8)	4909 (7.7)	
Age, mean (SD) [median] , y	46.6 (17.3) [49]	41.6 (16.2) [41]	41.8 (15.5) [42]	<0.001
Age, no. (%)				<0.001
18−34 y	2143 (29.2)	19,335 (37.6)	1823 (37.1)	
35−44 y	995 (13.6)	9613 (18.7)	843 (17.2)	
45−54 y	1577 (21.5)	10,492 (20.4)	1086 (22.1)	
55−64 y	1786 (24.3)	8661 (16.8)	856 (17.4)	
≥65 y	835 (11.4)	3379 (6.6)	301 (6.1)	
Female, no. (%)	3381 (46.1)	32,948 (64.0)	2686 (54.7)	<0.001
Region, no. (%)				<0.001
Midwest	703 (9.6)	8936 (17.4)	458 (9.3)	
Northeast	676 (9.2)	8147 (15.8)	337 (6.9)	
South	927 (12.6)	17,023 (33.1)	634 (12.9)	
West	288 (3.9)	4994 (9.7)	165 (3.4)	
Unknown (Medicaid)	4742 (64.6)	12,380 (24.0)	3315 (67.5)	
Race, no. (%)				<0.001
White	1320 (18.0)	7397 (14.4)	1468 (29.9)	
African American	2711 (37.0)	3033 (5.9)	1195 (24.3)	
Other	711 (9.7)	1950 (3.8)	652 (13.3)	
Unknown (commercial/Medicare supplemental)	2594 (35.4)	39,100 (76.0)	1594 (32.5)	
Insurance type, no. (%)				<0.001
Medicaid	4742 (64.6)	12,380 (24.0)	3315 (67.5)	
Commercial	1771 (24.1)	35,172 (68.3)	1270 (25.9)	
Medicare supplemental	823 (11.2)	3928 (7.6)	324 (6.6)	

BD-I = type I bipolar disorder; SCZ = schizophrenia.
* Difference among the overall cohorts (I, II, and III).
† The χ^2 test for categorical variables and t test for normally distributed continuous variables were used.

Table II. Baseline comorbidities.

Comorbidity	Cohort I: SCZ Alone (n = 7336)	Cohort II: BD-I Alone (n = 51,480)	Cohort III: Both SCZ and BD-I (n = 4909)	P*,†
Charlson Comorbidity Index, mean (SD)	1.1 (1.9)	0.9 (1.6)	1.4 (2.0)	<0.001
No. of chronic conditions, mean (SD)	3.1 (2.5)	3.2 (2.3)	4.1 (2.5)	<0.001
Psychiatric comorbidities	2659 (36.2%)	28,514 (55.4%)	3211 (65.4%)	<0.001
Major depressive disorder	1114 (15.2%)	14,798 (28.7%)	1379 (28.1%)	<0.001
Anxiety	1467 (20.0%)	19,133 (37.2%)	2141 (43.6%)	<0.001
Personality disorder	208 (2.8%)	1246 (2.4%)	583 (11.9%)	<0.001
Substance abuse disorders	961 (13.1%)	7583 (14.7%)	1653 (33.7%)	<0.001
Somatic comorbidities	3585 (48.9%)	22,284 (43.3%)	2845 (58.0%)	<0.001
Obesity	718 (9.8%)	5417 (10.5%)	851 (17.3%)	<0.001
Type 2 diabetes mellitus	1498 (20.4%)	6587 (12.8%)	1099 (22.4%)	<0.001
Hyperlipidemia	1926 (26.3%)	12,252 (23.8%)	1428 (29.1%)	<0.001
Hypertension	2757 (37.6%)	14,890 (28.9%)	2107 (42.9%)	<0.001
Any baseline inpatient hospitalization	1316 (17.9%)	9366 (18.2%)	2230 (45.4%)	<0.001

BD-I = type I bipolar disorder; SCZ = schizophrenia.
* Difference among the overall cohorts (I, II, and III).
† The χ^2 test for categorical variables and *t* test for normally distributed continuous variables were used.

psychiatric costs for patients with schizophrenia alone were $29,674 (95% CI, 28,485−30,863) and $13,329 (95% CI, 12,790−13,868); and mean all-cause and psychiatric costs for patients with BD-I alone were $27,292 (95% CI, 26,857−27,728) and $9306 (95% CI, 9108−9504).

In addition, we observed that patients with claims diagnoses of both schizophrenia and BD-I (cohort III) included 1.0% (n = 615) who met the BD-I criteria only in the year before meeting the schizophrenia criteria (cohort IIIa: BD-SCZ), 2.8% (n = 1794) who met schizophrenia criteria only in the year before, or on the same day as, meeting BD-I criteria (cohort IIIb: SCZ-BD), and 3.9% (n = 2500) who met BD-I criteria both in the year before and the year after meeting the schizophrenia criteria (cohort IIIc: BD-SCZ-BD). (See Supplemental Figure A1 in the online version at doi:10.1016/j.clinthera.2018.08.004 for study timelines for the 3 sub-cohorts of patients with diagnoses of both schizophrenia and BD-I based on claims.) Among the 1794 patients in cohort IIIb, 927 received both diagnoses on the same day. Of those occurring on the same day, the majority (83.4% [n = 773]) were based on claims from diagnoses given in hospital/emergency department settings. Specifically, 71.3% (n = 551), 19.1% (n = 148), and 9.6% (n = 74) received both diagnoses in an inpatient hospital, outpatient hospital, and emergency department setting, respectively.

In the sensitivity analysis, we found that even after excluding patients with schizoaffective disorder, those with diagnoses of both schizophrenia and BD-I based on claims had the highest hospitalization rates and all-cause health care costs in the 1-year follow-up period compared with patients with either condition alone (ie, schizophrenia alone or BD-I alone) (see Supplemental Figures A2 and A3 in the online version at https://doi.org/10.1016/j.clinthera.2018.08.004).

DISCUSSION

Despite the fact that schizophrenia and BD are separate psychiatric disorders, when examining real-world

Table III. Medication use.

Variable	Cohort I: SCZ alone (n = 7336)	Cohort II: BD-I Alone (n = 51,480)	Cohort III: Both SCZ and BD-I (n = 4909)	P*,†
Baseline medication use				
Atypical and typical antipsychotic agents, no. (%)	4073 (55.5)	16,330 (31.7)	3743 (76.2)	<0.001
Oral antipsychotic agent, no. (%)	3868 (52.7)	15,982 (31.0)	3641 (74.2)	<0.001
LAI, no. (%)	447 (6.1)	179 (0.3)	361 (7.4)	<0.001
Psychiatric medications, no. (%)	3892 (53.1)	38,071 (74.0)	3842 (78.3)	<0.001
Somatic medications, no. (%)	3142 (42.8)	20,997 (40.8)	2448 (49.9)	<0.001
One-year postindex medication use				
N	7336	51,480	4909	
Atypical and typical antipsychotic agents, no. (%)	5749 (78.4)	26,845 (52.1)	4253 (86.6)	<0.001
Oral antipsychotic agent, no. (%)	5442 (74.2)	26,500 (51.5)	4123 (84.0)	<0.001
LAI, no. (%)	983 (13.4)	387 (0.8)	639 (13.0)	<0.001
Psychiatric medications, no. (%)	4941 (67.4)	43,957 (85.4)	4161 (84.8)	<0.001
Somatic medications, no. (%)	3950 (53.8)	24,064 (46.7)	2786 (56.8)	<0.001

BD-I = type I bipolar disorder; LAI = long-acting injectable antipsychotic agent; SCZ = schizophrenia.
* Difference among the overall cohorts (I, II, and III).
† The χ^2 test for categorical variables and *t* test for normally distributed continuous variables were used.

claims data, we found evidence of diagnostic uncertainty, as almost 8% of patients in a large nationally representative sample had received both diagnoses based on claims within a 2.5-year period. Almost 19% of patients with both diagnoses received them on the same day. Of those occurring on the same day, the majority (>80%) were based on claims from the hospital or emergency department setting.

Our findings are supported by several theories and studies. Schizophrenia and BD-I share common suspected etiologic agents, as risk factors for both include genetic and environmental factors,[17] social problems,[24] obstetric complications,[25] medication use,[26] migrant status,[27] and infectious agents.[28] Patients with BD-I may experience psychotic symptoms during manic or depressive episodes, and patients with schizophrenia can experience manic or depressive episodes between or during psychotic episodes. A large cohort study with administrative data on almost 1 million veterans in the United States found that 7% of veterans with schizophrenia also had a qualifying diagnosis of BD-I (at least 1 inpatient or 2 outpatient claims).[29] A study by Fountoulakis et al[12] found that among a sample of 175 stabilized patients with schizophrenia, more than one quarter experienced significant manic symptoms. According to the authors, these findings suggest that a number of patients diagnosed with schizophrenia actually have a form of BD with psychotic symptoms.[12] These studies and others, including ours, suggest that psychiatric multimorbidity is common.[13]

Emil Kraepelin, who developed the core concepts of schizophrenia and BD, reported that in his clinical experience, there were patients with features of both diseases.[30] Several clinicians and researchers have claimed that schizophrenia and BD are the same disorder within a broad continuum, with nonpsychotic mood disorders at one end and psychotic disorders at the opposite end.[9,12,31,32] A study by Laursen et al,[9] in which investigators examined clinical diagnoses of schizophrenia and BD in the entire Danish population over a 35-year period, showed a substantial overlap between the diseases, particularly in the younger patients; the authors challenged the

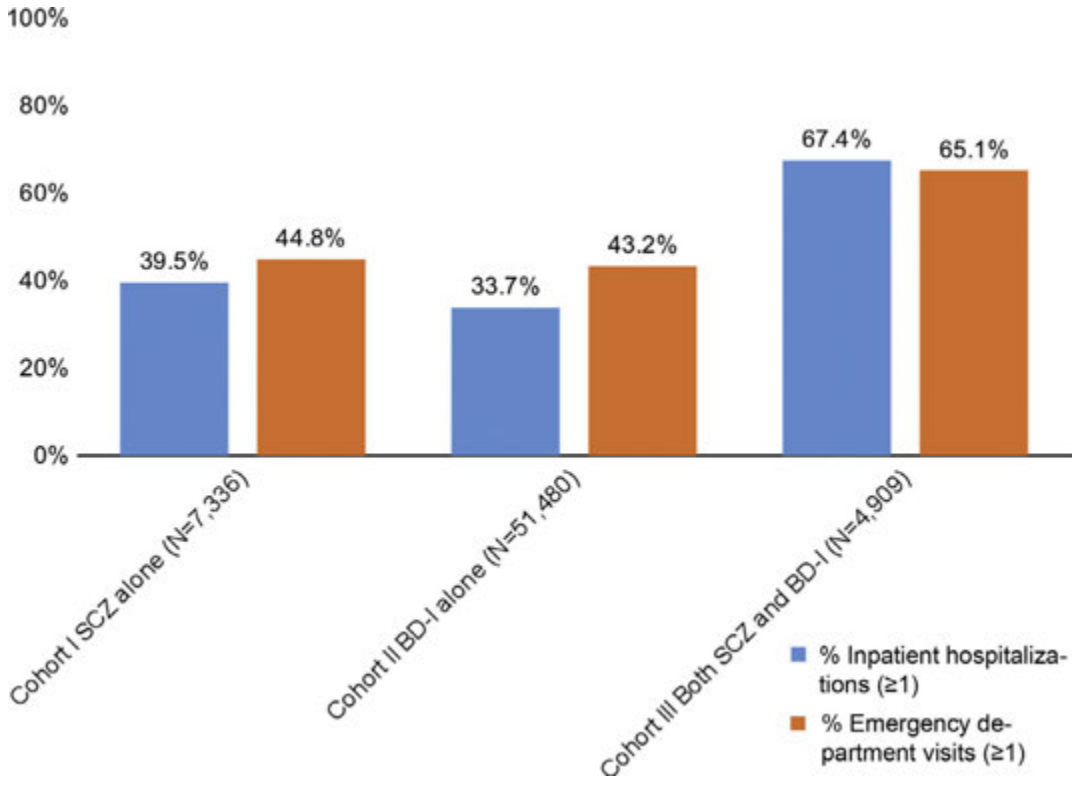

Figure 2. Unadjusted all-cause hospitalization and emergency department visit rates during the 1-year follow-up period (all $P < 0.001$ for comparisons across groups). The mean rates of all-cause hospitalization and emergency department visits were highest in cohort III (both schizophrenia [SCZ] and type I bipolar disorder [BD-I]) compared with cohort I (SCZ alone) and cohort II (BD-I alone).

stringent categorical approach to these disorders used in both the DSM and ICD classification systems.

In the present study, patients with different diagnoses and different diagnosis patterns, based on claims, varied significantly in demographic characteristics, disease burden, medication use, health care resource utilization, and health care costs. Specifically, patients with claims for both diagnoses (cohort III) had the following: (1) more chronic conditions and substance abuse disorders; (2) higher rates of atypical and typical antipsychotic medication use in the 1-year postindex period; (3) higher rates of all-cause and psychiatric health care resource utilization in the 1-year postindex period; and (4) higher all-cause and psychiatric health care costs in the 1-year postindex period compared with patients with schizophrenia alone (cohort I) and BD-I alone (cohort II). Risk-adjusted models suggest that differences in health care utilization and costs among the 3 cohorts were not due to differences in insurance type, age, or sex and that patients with both diagnoses may be generally sicker and require more health care services. Increased substance abuse among these patients also likely contributes to their increased disease burden and health care utilization. In general, our study, along with other previous research, suggests that psychiatric multimorbidity is associated with clinical differences and increased complexity compared with patients with psychiatric monomorbidity.[13]

Our finding that >67% of patients with claims-based diagnoses of both schizophrenia and BD-I had at least 1 hospitalization in the 1-year period after diagnosis is a new finding, but it is in line with previous results that 66.5% of patients with schizophrenia and 81.4% of patients with BD-I had a hospitalization in 1 year.[8] We show mean all-cause health care costs of $51,085 among patients with both schizophrenia and BD-I, also a novel finding. Patients in our study with BD-I alone had mean all-cause health care costs of $26,396 per patient compared with $18,759 estimated in the study by Cloutier et

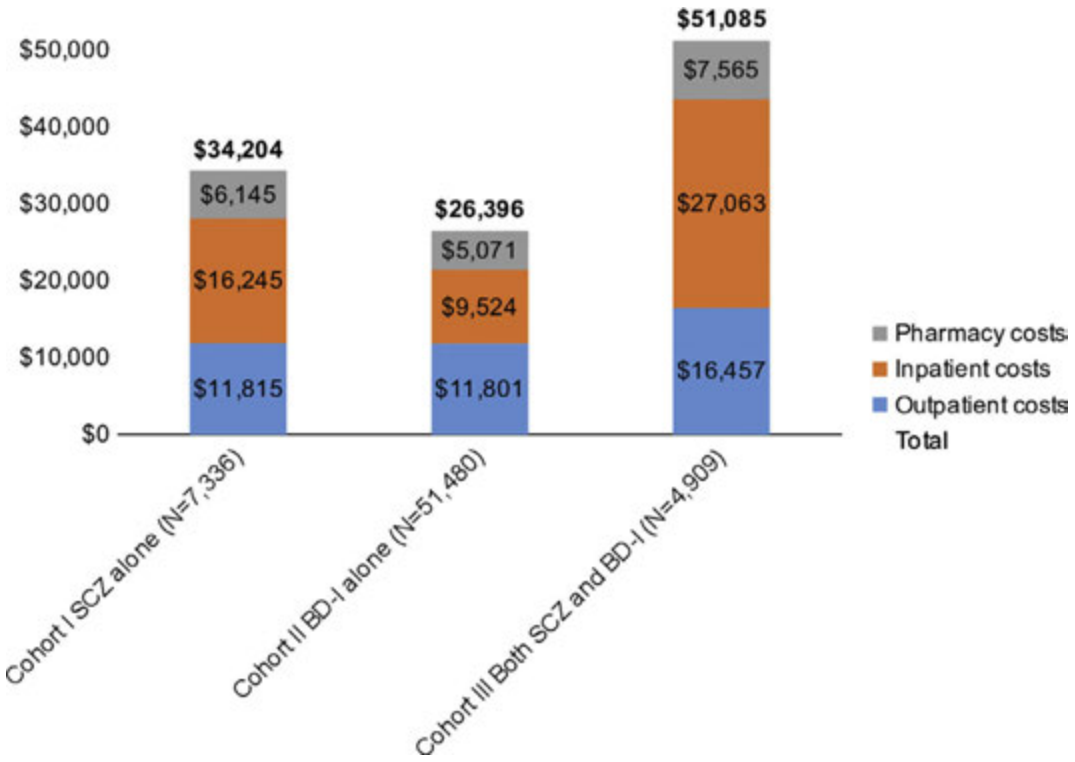

Figure 3. Unadjusted all-cause mean health care costs during the 1-year follow-up period (adjusted to 2016 US dollars); all $P < 0.001$ for comparisons across groups. All-cause and psychiatric health care costs were highest in cohort III (both schizophrenia [SCZ] and type I bipolar disorder [BD-I]) compared with cohort I (SCZ alone) and cohort II (BD-I alone).

al.[3] These health care cost estimates for patients with BD-I alone may differ because: (1) our cost estimate was reported in 2016 US dollars, whereas Cloutier et al expressed cost in 2015 US dollars; and (2) we used 4.5 years of data (from 2012–2016), whereas Cloutier et al estimated economic burden for the year 2015. Patients in our study with schizophrenia alone had mean all-cause health care costs of $34,204 per patient compared with $22,338 estimated in the study by Huang et al.[5] Our estimate of health care costs for patients with schizophrenia may be higher than that reported by Huang et al because of differences in patient populations, as the majority of patients in our study were receiving Medicaid and those in the study by Huang et al had private insurance.

Among patients without schizoaffective disorder in the present study, those with diagnoses of both schizophrenia and BD-I based on claims had the highest hospitalization rates and all-cause health care costs in the 1-year follow-up period compared with patients with either diagnosis alone (ie, schizophrenia alone or BD-I alone). Furthermore, patients with schizoaffective disorder and diagnoses of both schizophrenia and BD-I based on claims had even higher hospitalization rates, all-cause health care costs, and comorbidities than patients without schizoaffective disorder (results available upon request). Future studies could examine the additive contribution of each comorbidity to health care utilization and costs in schizophrenia and BD-I.

No study to date has examined characteristics, health care resource use, and health care costs in patients with new episodes of both schizophrenia and BD-I. We identified differential patient characteristics, health care resource utilization, and costs among the cohorts, and we took the first steps to investigate these groups. Also, this study may suggest the need to revisit the diagnostic algorithms commonly used in claims data for identifying patients with schizophrenia and BD, as our finding that almost 8% of patients received both diagnoses based on claims, and almost 19% of those patients received both diagnoses on the same day, does not fit with clinical knowledge (ie, while patients may not have both diseases, their symptoms are unclear and may include components

from both diseases). There has been an approach used by the US Department of Veterans Affairs to categorize patients who met the claims-based diagnostic criteria for both schizophrenia and BD into a single diagnostic group (ie, either schizophrenia or BD).[29] Specifically, in a large comprehensive assessment of the Veterans Health Administration Mental Health Program, patients were categorized into either the schizophrenia or BD diagnostic group based on the modal frequency of diagnosis codes. There are diagnostic challenges, but regardless of the underlying disease, patients with multiple claims–based diagnoses are fundamentally different from patients with a single claims–based diagnosis.

Given that numerous studies use the claims-based diagnostic algorithms employed for our analyses, a clinical validation study would be useful to determine if patients receive both diagnoses more commonly than suspected, and to either validate the commonly used claims-based algorithms or determine if changes to the algorithms are needed to adequately identify a meaningful cohort for analysis. The currently used structured diagnostic algorithms could oversimplify the complexities associated with psychopathology and clinical care.[13]

This study has limitations. First, claims data used for this analysis are generated for reimbursement, not research, and coding errors, misclassification, diagnostic uncertainty, and/or omissions could affect the reliability of the findings. Specifically, we could not clinically validate any diagnoses in this study due to privacy regulations, as data were de-identified, and thus diagnostic assignments may be inaccurate. Nevertheless, health insurance claims data remain a valuable source of information because they contain a large and valid sample of patient characteristics in a real-world setting. Second, this study was an exploratory trial, but the findings provide a foundation for hypothesis testing in future research. For example, we are considering more extensive risk adjustment, or different modeling techniques, that would allow us to control for clinical characteristics. Third, we did not have information about the diagnosing physician's specialty, as it was only available in ~10% of the claims. We attempted to examine the diagnosing physician's specialty based on the theory that diagnoses by psychiatrists would likely be more reliable than diagnoses from other specialists. Lastly, we did not include patients who were Medicare and Medicaid dual eligible, which may explain the smaller ratio of schizophrenia to BD-I patients we found compared with the national rate, as a larger percentage of patients with schizophrenia have dual eligibility than the US general population.[33]

CONCLUSIONS

This study is the first real-world, nationally representative trial to examine characteristics, health care resource use, and costs in patients with new episodes of schizophrenia and BD-I based on claims. We found evidence of diagnostic uncertainty in claims data, as almost 8% of patients had received both diagnoses in a 2.5-year period, which does not align with clinical knowledge. Patients with a diagnosis of both schizophrenia and BD-I were generally sicker and required more health care services compared with patients with either diagnosis alone. We identified differential characteristics, health care resource use, and costs among the cohorts.

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All authors met the International Committee of Medical Journal Editors criteria for authorship, including equal contributions to study concepts and design, interpretation of the data, and to the drafting and critical review of the manuscript. Dr. Chang further contributed to the analysis of the data. The manuscript was read and approved by all authors.

CONFLICTS OF INTEREST

Drs. Broder, Chang, Munday, and Yan are employees of PHAR, LLC, which was paid by Otsuka and Lundbeck to perform the research described in this article. Dr. Greene is an employee of Otsuka. Drs. Hartry and Touya are employees of Lundbeck. The authors have indicated that they have no other conflicts of interest regarding the content of this article. The study sponsor collaborated with authors and contributed to study concept and design, interpretation of the data, and drafting and critical review of the manuscript.

SUPPLEMENTARY MATERIALS

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