CURRENT MEDICAL RESEARCH AND OPINION
https://doi.org/10.1080/03007995.2019.1571295
Article FT-0609.R1/1571295

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Early initiation of long-acting injectable antipsychotic treatment is associated with lower hospitalization rates and healthcare costs in patients with schizophrenia: real-world evidence from US claims data

Jennifer Munday[a], Mallik Greene[b], Eunice Chang[a], Ann Hartry[c], Tingjian Yan[a] and Michael S. Broder[a]

[a]Health Services Research, Partnership for Health Analytic Research, LLC, Beverly Hills, CA, USA; [b]Health Economics & Outcomes Research, Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, NJ, USA; [c]Health Economics and Outcomes, Lundbeck, LLC, Deerfield, IL, USA

ABSTRACT

Objective: Early initiation of antipsychotic treatment in schizophrenia is associated with improved outcomes. This study aimed to determine if initiation of long-acting injectable (LAI) antipsychotic treatment early in a new schizophrenia episode is associated with lower hospitalization rates and healthcare costs in a real-world setting.

Methods: This retrospective (January 1, 2007–June 30, 2016) cohort analysis used claims from Truven Health Analytics MarketScan Commercial, Medicaid, and Medicare Supplemental databases. In adults ≥18 years with a new episode of schizophrenia, two mutually exclusive cohorts were identified based on time from first recorded schizophrenia diagnosis date to first date of LAI initiation (index date): ≤1 year (early initiators) and >1 year (late initiators). Logistic and general linear regression models were performed to estimate adjusted hospitalization rate and healthcare costs in a 1-year follow-up, controlling patient demographic and clinical characteristics, insurance type, baseline all-cause hospitalizations and ED visits, and baseline psychiatric medication use.

Results: Of the subjects, 32% ($n = 1388$) initiated treatment early and 68% ($n = 2978$) initiated treatment later. In risk-adjusted models, all-cause hospitalization rates were 22.2% (95% CI = 19.9–24.6%) in early initiators and 26.9% (95% CI = 25.2–28.7%) in late initiators ($p = .002$). Of early initiators, 14.1% (95% CI = 12.3–16.1%) had a psychiatric hospitalization vs 19.2% (95% CI = 17.7–20.8%) of late initiators ($p < .001$). Adjusted psychiatric healthcare costs were significantly lower in early initiators compared with late initiators [mean (95% CI) = $21,545 (20,355–22,734) vs $24,132 (23,330–24,933)] ($p < .001$).

Conclusions: LAI initiation within 1 year of a new schizophrenia episode led to lower hospitalization rates and healthcare costs compared with LAI initiation more than 1 year after a new episode.

ARTICLE HISTORY
Received 3 August 2018
Revised 11 January 2019
Accepted 15 January 2019

KEYWORDS
Long-acting injectable antipsychotics; Schizophrenia; Healthcare utilization; Healthcare cost

Introduction

Schizophrenia is a severe, disabling psychiatric disorder affecting less than 1% of the adult population in the US in a given year[1,2]. The disease is characterized by positive symptoms (e.g. hallucinations, delusions, thought disorders, etc.), negative symptoms (e.g. flat affect, reduced feelings of pleasure, etc.), and cognitive symptoms[2]. The estimated annual direct and indirect costs associated with schizophrenia were over $155 billion in 2013[3]. Antipsychotic treatment is the cornerstone of management for patients with schizophrenia[4,5]. Treatment guidelines published by the American Psychiatric Association recommend that first-episode schizophrenia be treated with oral antipsychotics and long-acting injectable (LAI) antipsychotics should be reserved for non-compliant patients with chronic schizophrenia[6].

Early initiation of antipsychotic treatment is associated with enhanced treatment response and prognosis, and reduced symptoms, relapse (i.e. hospitalizations, failure to respond, failure to improve, and psychotic exacerbations), healthcare resource use, and costs[7–10]. However, even well-timed treatment is ineffective if patients are not adherent to their medications[11,12], and non-adherence is a significant problem in this disease. Rates of non-adherence to schizophrenia medication range from 34–81%, depending on the method of assessment and metric used, with many studies reporting rates around 50%[13–19]. Previous studies have shown that antipsychotic non-adherence and drug formulation (e.g. oral vs LAI) predict an increased risk of hospitalization[20]. Improving adherence results in reduced hospitalizations, and, in turn, healthcare savings[21–23]. LAI formulations of antipsychotics are consistently shown to improve adherence compared to oral ones[24,25], despite a mixed impact on other health outcomes, such as relapse[26].

Early effective antipsychotic treatment, initiated at a stage of the illness during which psychosocial and structural damage may be less extensive, may be neuroprotective, and

CONTACT Mallik Greene mallik.greene@otsuka-us.com Health Economics & Outcomes Research, Otsuka Pharmaceutical Development & Commercialization, Inc., 508 Carnegie Center, Princeton, NJ 08540, USA

better adherence may lead to longer-term treatment effects[27]. LAIs are increasingly being advocated for as early intervention or first-episode treatment for schizophrenia due to the superior adherence and other health benefits, such as improved functioning[28], associated with this formulation[28–35].

In a search of the literature in 2018 using PubMed, there were no prior nationally representative studies that examined healthcare utilization or cost outcomes associated with timing of LAI initiation in patients with schizophrenia. Most studies that have assessed similar outcomes focused on differences between oral antipsychotic treatment and LAI treatment. Using insurance claims data, in this study, we examined whether patients with new episodes of schizophrenia who receive LAI treatment soon after a claims diagnosis have lower hospitalization rates and healthcare costs compared with patients who receive LAI treatment later, regardless of prior oral antipsychotic medication use. Given that LAIs have proven efficacious, we hypothesized that initiation of LAIs soon after a new schizophrenia episode would be superior to later LAI treatment initiation from an economic standpoint.

Methods

Data sources

Data from the Truven Health Analytics MarketScan Medicaid, commercial, and Medicare supplemental databases from January 1, 2007 to June 30, 2016 were used. The MarketScan Medicaid, commercial, and Medicare supplemental databases are Health Insurance Portability and Accountability Act (HIPAA)-compliant administrative claims databases.

The Medicaid database contains the pooled healthcare experience of approximately 40 million Medicaid enrollees from multiple US 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 (such as ethnicity, maintenance assistance status, and Medicare eligibility). The names of the specific states are not available in the Truven Medicaid database.

The commercial data included medical encounters from ~ 65 million individuals and their dependents insured by employer-sponsored plans (i.e. non-Medicare eligible) in the US 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 about 5.3 million Medicare-eligible retired employees and their spouses with employer-sponsored Medicare supplemental plans in the US. Given the de-identified nature of the data used in the present study, informed consent was not required by HIPAA rules.

Study population and measures

In this study, we classified patients into two groups based on time from diagnosis to LAI initiation: ≤1 year (early) and >1 year (late). We identified patients with new episodes of schizophrenia in that they did not have a claim identified with schizophrenia in the preceding year. Patients were deemed to have a diagnosis of schizophrenia if they had at least one inpatient claim or at least two outpatient claims (on separate dates) for schizophrenia disorders (International Classification of Disease, 9th Revision, Clinical Modification [ICD-9-CM] code: 295.xx, excluding 295.4x and 295.7x; or 10th revision [ICD-10-CM] code: F20x, excluding F20.81x). Therefore, we use the term "diagnosis" to denote that a patient met the claims-based criteria for a disease of interest (i.e. they received at least one inpatient claim or at least two outpatient claims for the disease).

Patients with schizophrenia were required to have (1) received an LAI in the study identification (ID) period between January 1, 2008 and June 30,2015, and (2) a diagnosis date prior to or on the first date they received an LAI. The first date of the LAI was defined as the index date. To ensure that we were examining new episodes of care, patients were excluded if they had any medical claims for schizophrenia in the 1-year prior to their first diagnosis date found in the study ID period. To ensure we were examining initiation of an LAI for the first time in a given episode, patients with LAI use in the 1 year prior to the index date were excluded (see Figure 1).

We excluded patients who had a prescription for clozapine anytime during the study period, since clozapine is indicated for treatment of severely ill patients with schizophrenia who fail to respond adequately to standard antipsychotic treatments. We required patients to be ≥18 years on the index date and have continuous health plan enrollment for 1 year prior to (baseline) and after (follow-up) the index date. Due to incomplete data, we further excluded patients who had Medicare and Medicaid dual eligibility; had capitated insurance plans among Medicaid enrollees; lacked pharmacy coverage; or lacked mental health coverage during the entire study period.

Patient characteristics examined included demographic variables (e.g. age, sex, geographic region, race); insurance type; Charlson Comorbidity Index (CCI)[36]; number of chronic condition indicators[37]; comorbidities; medication use (baseline and 1 year post-index); healthcare utilization at baseline, including all-cause and psychiatric office visits, inpatient hospitalizations, and emergency department visits; and costs at baseline, including all-cause and psychiatric total, inpatient, outpatient, and pharmacy. Healthcare costs were adjusted to 2016 US dollars.

Outcomes examined were (1) the number of all-cause and psychiatric inpatient hospitalizations over the 1-year follow-up period; and (2) all-cause and psychiatric total healthcare costs, including costs from inpatient, outpatient, and pharmacy settings over the 1-year follow-up period.

Statistical analysis

Descriptive statistics, including means, standard deviations, and relative frequencies and percentages for continuous and categorical data, respectively, were reported. Additionally, *t*-tests,

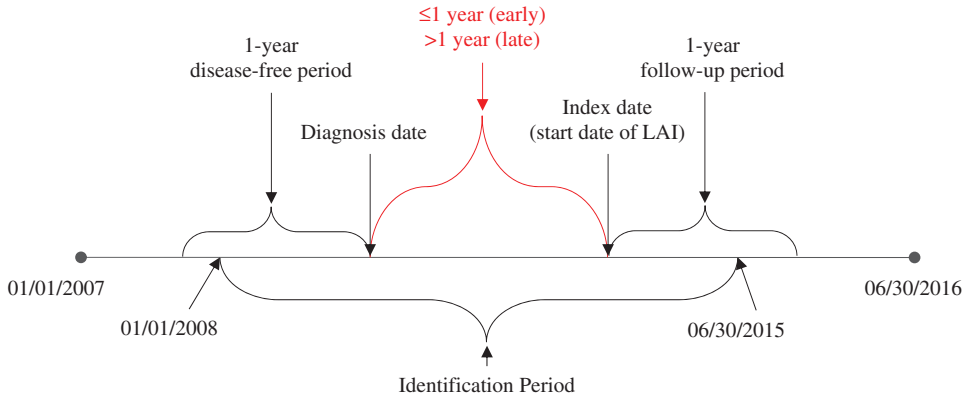

Figure 1. Study timeline. Patients with schizophrenia were classified into two groups based on time from diagnosis to LAI initiation: ≤1 year (early) and >1 year (late). Patients were required to be disease free for a year prior to diagnosis (≥1 inpatient claim or ≥2 outpatient claims for disease) date, and to have received an LAI during the study identification period (January 1, 2008 to June 30, 2015). The index date was defined as the first date of LAI. The baseline and follow-up periods were defined as the 1 year before and after the index date, respectively.

Chi-square, and Wilcoxon rank sum tests were performed depending on the type of measure. Logistic regression models were conducted to examine the association between each hospitalization and timing of LAI initiation; and linear regression models were conducted to examine the association between costs and timing of LAI initiation. Because the dichotomous variable cutoff of 1 year was arbitrary, we conducted sensitivity analyses using time between diagnosis and LAI as a continuous independent variable. We also ran models using the quadratic term of time from diagnosis to LAI to determine if any relationship was non-linear. All models were adjusted for baseline patient demographic and clinical characteristics (i.e. age, gender, mean CCI score, number of chronic conditions, psychiatric comorbidities, hyperlipidemia and hypertension), insurance type, all-cause hospitalizations and emergency department visits at baseline, and psychiatric medication use at baseline (including number of oral antipsychotic used). All data transformations and statistical analyses were performed using SAS version 9.4.

Results

Baseline patient demographics, comorbidities, healthcare utilization, and costs

Of the 117,792 patients with a claims-based diagnosis of schizophrenia from January 1, 2008 to June 30, 2015, 11,936 initiated an LAI after diagnosis (see Figure 2). The final study sample included 4366 patients (≥18 years) with new episodes of schizophrenia who initiated an LAI after the onset of the episode. As shown in Table 1, 31.8% ($n = 1388$) of patients initiated an LAI within 1 year following a new schizophrenia episode (early initiators), and 68.2% ($n = 2978$) initiated an LAI more than 1 year following a new schizophrenia episode (late initiators). Early initiators had a mean (SD) of 4.7 (3.9) months between the new schizophrenia episode and initiation of LAI treatment (index date). Late initiators had a mean (SD) of 2.8 (1.25) years between the new schizophrenia episode and initiation of LAI treatment. Early initiators were younger, more likely to have commercial health insurance, had a lower burden of chronic diseases (e.g. obesity, type 2 diabetes, hyperlipidemia, hypertension), had a higher rate of major depressive disorders, and fewer used other psychiatric medications compared with late initiators (all $p < .05$) (Table 1).

At baseline, early initiators, compared with late initiators, had fewer all-cause and psychiatric office visits [all-cause mean (SD) = 9.9 (15.6) vs 21.4 (34.6); psychiatric mean (SD) = 6.5 (13.3) vs 16.2 (32.5)], more all-cause and psychiatric inpatient hospitalizations [all-cause n (%) = 787 (56.7) vs 1325 (44.5); psychiatric n (%) = 691 (49.8) vs 1150 (38.6)], and more all-cause and psychiatric emergency department visits [all-cause n (%) = 661 (47.6) vs 1123 (37.7); psychiatric n (%) = 366 (26.4) vs 664 (22.3)] (all $p < .05$). All-cause costs did not significantly differ between early and late initiators. However, psychiatric costs were significantly lower after initiating an LAI among early initiators [mean (SD) = $20,531 (29,254) vs $24,855 (27,684); $p < .001$].

Adjusted hospitalizations

As shown in Table 2, CCI, number of chronic conditions, having at least one inpatient hospitalization, at least one emergency department visit, bipolar I disorder (BD-I) claim, MDD, anxiety, and taking an oral antipsychotic medication at baseline significantly increased patients' risk of all-cause and psychiatric hospitalization in the 1-year follow-up period (all $p < .05$). Early initiation of LAI treatment, compared with late initiation, was associated with a 23% reduced risk of all-cause hospitalization and a 31% reduced risk of psychiatric hospitalization (all $p < .05$).

As shown in Figure 3, early LAI initiators had fewer all-cause and psychiatric hospitalizations compared with late LAI initiators in the 1-year follow-up period. Specifically, in risk-adjusted models, 22.2% (95% CI = 19.9–24.6%) of early initiators had an all-cause hospitalization compared with 26.9% (95% CI = 25.2–28.7%) of late initiators ($p = .002$); and 14.1% (95% CI = 12.3–16.1%) of early initiators had a psychiatric hospitalization compared with 19.2% (95% CI = 17.7–20.8%) of late initiators ($p < .001$).

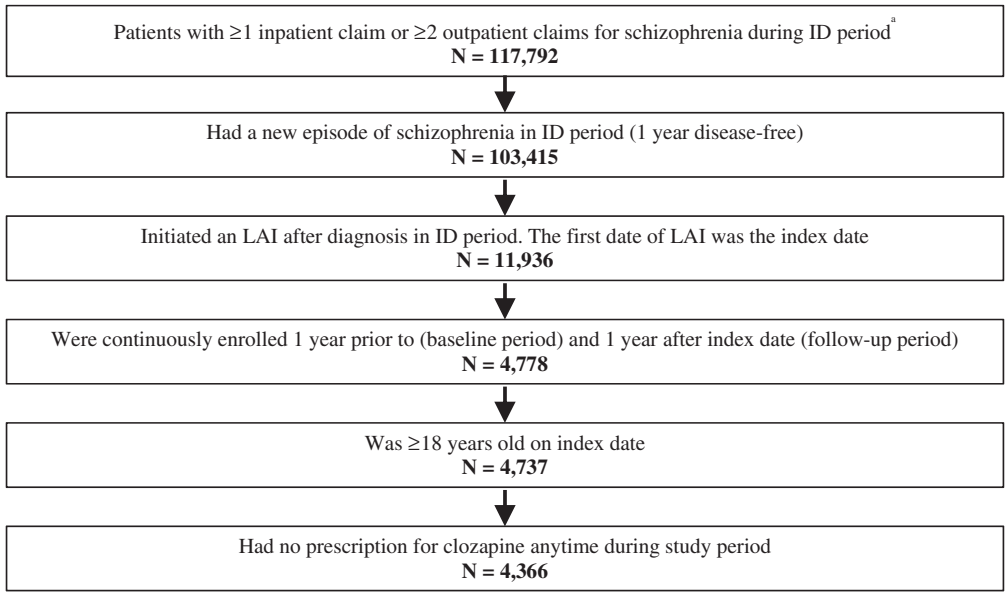

Figure 2. Patient attrition. A total of 117,792 patients with a claims-based diagnosis of schizophrenia from [a]January 1, 2008 to June 30, 2015 were identified, and, of these, 11,936 initiated an LAI after diagnosis. After applying additional exclusion criteria, the final study sample included 4366 patients (≥18 years) with new episodes of schizophrenia who initiated an LAI after the onset of the episode.

Table 1. Patient demographics, comorbidities, and baseline medications.

	Time from diagnosis to LAI initiation			
	≤1 year	>1 year	All patients	*p*-value[a]
n (%)	1388 (31.8)	2978 (68.2)	4366 (100.0)	
Age, years, mean (SD) [median]	38.8 (15.8) [36]	41.3 (14.0) [41]	40.5 (14.7) [40]	<.001
Age, years, *n* (%)				<.001
18–34	668 (48.1)	1146 (38.5)	1814 (41.5)	
35–44	197 (14.2)	534 (17.9)	731 (16.7)	
45–54	244 (17.6)	700 (23.5)	944 (21.6)	
55–64	212 (15.3)	502 (16.9)	714 (16.4)	
65+	67 (4.8)	96 (3.2)	163 (3.7)	
Female, *n* (%)	568 (40.9)	1213 (40.7)	1781 (40.8)	.905
Region, *n* (%)				<.001
Midwest	128 (9.2)	153 (5.1)	281 (6.4)	
Northeast	79 (5.7)	108 (3.6)	187 (4.3)	
South	165 (11.9)	144 (4.8)	309 (7.1)	
West	34 (2.4)	43 (1.4)	77 (1.8)	
Unknown (Medicaid)	982 (70.7)	2530 (85.0)	3512 (80.4)	
Race, *n* (%)				<.001
White	278 (20.0)	809 (27.2)	1087 (24.9)	
African American	555 (40.0)	1444 (48.5)	1999 (45.8)	
Other	149 (10.7)	277 (9.3)	426 (9.8)	
Unknown (Commercial/Medicare supplemental)	406 (29.3)	448 (15.0)	854 (19.6)	
Insurance type, *n* (%)				<.001
Medicaid	982 (70.7)	2530 (85.0)	3512 (80.4)	
Commercial	328 (23.6)	345 (11.6)	673 (15.4)	
Medicare supplemental	78 (5.6)	103 (3.5)	181 (4.1)	
Charlson comorbidity Index, mean (SD)	0.9 (1.5)	1.0 (1.6)	1.0 (1.6)	.009
No. chronic conditions, mean (SD)	3.2 (2.1)	3.5 (2.2)	3.4 (2.2)	<.001
Bipolar I disorder, *n* (%)	520 (37.5)	1081 (36.3)	1601 (36.7)	.457
Major depressive disorder, *n* (%)	315 (22.7)	531 (17.8)	846 (19.4)	<.001
Anxiety, *n* (%)	442 (31.8)	862 (28.9)	1304 (29.9)	.051
Personality disorder, *n* (%)	176 (12.7)	405 (13.6)	581 (13.3)	.405
Substance abuse disorders, *n* (%)	497 (35.8)	1001 (33.6)	1498 (34.3)	.155
Somatic comorbidities, *n* (%)	669 (48.2)	1679 (56.4)	2348 (53.8)	<.001
Obesity	186 (13.4)	494 (16.6)	680 (15.6)	.007
Diabetes mellitus Type 2	244 (17.6)	701 (23.5)	945 (21.6)	<.001
Hyperlipidemia	283 (20.4)	899 (30.2)	1182 (27.1)	<.001
Hypertension	494 (35.6)	1256 (42.2)	1750 (40.1)	<.001
Oral antipsychotic medication, *n* (%)	990 (71.3)	2375 (79.8)	3365 (77.1)	<.001
Psychiatric medications, *n* (%)	881 (63.5)	2073 (69.6)	2954 (67.7)	<.001
Somatic medications, *n* (%)	510 (36.7)	1383 (46.4)	1893 (43.4)	<.001

[a]Difference among the two groups.

Table 2. Odds ratios[a] of all-cause and psychiatric[b] inpatient hospitalizations in the 1-year follow-up period.

	Any inpatient hospitalization in post 1-year period		Any psychiatric-specific inpatient hospitalization in post 1-year period	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age group				
18–34 vs 55+	1.24 (0.97–1.58)	.091	1.69 (1.28–2.23)	<.001
35–44 vs 55+	0.90 (0.69–1.17)	.429	1.09 (0.80–1.47)	.583
45–54 vs 55+	0.92 (0.72–1.16)	.470	1.04 (0.79–1.37)	.802
Female vs Male	1.02 (0.87–1.19)	.832	0.92 (0.77–1.09)	.346
Insurance type				
Medicaid vs Commercial	0.95 (0.77–1.17)	.643	0.82 (0.66–1.02)	.080
Medicare Supplemental vs Commercial	1.16 (0.78–1.74)	.465	0.97 (0.61–1.53)	.884
Charlson Comorbidity Index	1.14 (1.08–1.21)	<.001	1.08 (1.02–1.14)	.009
No. Chronic Conditions (HCUP)	1.10 (1.04–1.16)	<.001	1.03 (0.97–1.09)	.322
Baseline hypertension (y vs n)	1.00 (0.83–1.21)	.998	0.98 (0.80–1.21)	.882
Baseline hyperlipidemia (y vs n)	0.87 (0.73–1.05)	.143	0.92 (0.75–1.13)	.431
Baseline inpatient hospitalization (y vs n)	2.04 (1.72–2.42)	<.001	2.55 (2.10–3.10)	<.001
Baseline emergency department visit (y vs n)	1.51 (1.30–1.76)	<.001	1.59 (1.34–1.87)	<.001
Baseline type 1 bipolar disorder (y vs n)	1.44 (1.23–1.69)	<.001	1.45 (1.22–1.73)	<.001
Baseline major depressive disorder (y vs n)	1.32 (1.11–1.58)	.002	1.39 (1.15–1.67)	<.001
Baseline anxiety (y vs n)	1.26 (1.06–1.48)	.007	1.34 (1.12–1.59)	.001
Baseline personality disorder (y vs n)	1.12 (0.91–1.37)	.285	1.14 (0.92–1.41)	.221
Baseline substance abuse disorder (y vs n)	1.10 (0.93–1.29)	.259	1.09 (0.91–1.29)	.348
Baseline psychiatric medication Use (y vs n)	1.05 (0.88–1.27)	.568	1.16 (0.94–1.42)	.169
Number of baseline oral antipsychotic medication used	1.17 (1.10–1.25)	<.001	1.17 (1.09–1.26)	<.001
Early vs late LAI initiation	0.77 (0.66–0.91)	.002	0.69 (0.58–0.83)	<.001

[a]Adjusted by baseline characteristics [age group, gender, insurance type, Charlson comorbidity index, no. of chronic conditions (HCUP), baseline hypertension, baseline hyperlipidemia, baseline comorbidities (including type 1 BD, MDD, anxiety, personality disorder, substance abuse disorder)], baseline inpatient hospitalization, baseline psychiatric medication use, and number of baseline oral antipsychotic medication used.
[b]Claims with a primary diagnosis of any mental disorder (ICD-9-CM: 290.xx-311.xx; ICD-10-CM code: F01.xx-F99.xx).

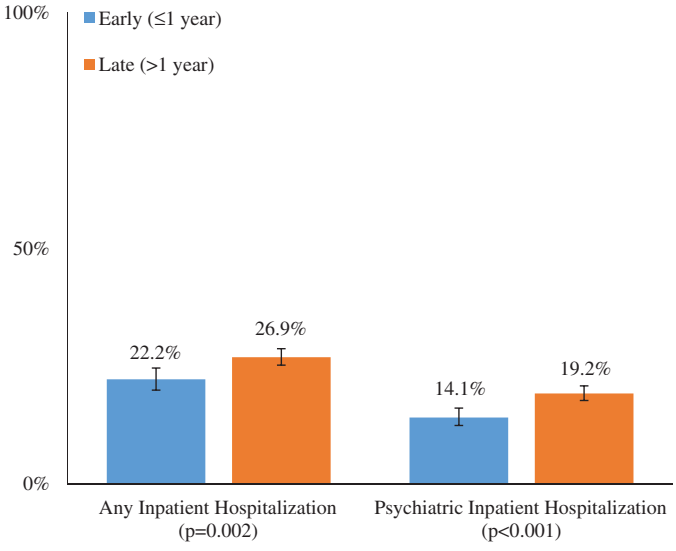

Figure 3. Risk adjusted[a] rates of all-cause and psychiatric[b] hospitalizations in the 1-year follow-up period. Early LAI initiators had fewer all-cause and psychiatric hospitalizations compared with late LAI initiators in the 1-year follow-up period.
[a]Adjusted by baseline characteristics [age group, gender, insurance type, Charlson comorbidity index, no. of chronic conditions (HCUP), baseline hypertension, baseline hyperlipidemia, baseline comorbidities (including type 1 BD, MDD, anxiety, personality disorder, substance abuse disorder)], baseline inpatient hospitalization, baseline psychiatric medication use, and number of baseline oral antipsychotic medication used.
[b]Costs of claims with a primary diagnosis of any mental disorder (ICD-9-CM: 290.xx-311.xx; ICD-10-CM code: F01.xx-F99.xx), and costs of mental health-related treatments

Adjusted healthcare costs

As shown in Table 3, insurance type, CCI, number of chronic conditions, having at least one baseline ED visit, having at least one BD-I claim, personality disorder, substance abuse disorder, psychiatric medication use, and oral antipsychotic medication use were statistically significantly associated with all-cause costs among all patients with schizophrenia (all $p < .05$). For example, having a claim for BD-I was associated with a $4306 increase in all-cause costs compared to patients without a claim for BD-I ($p = .002$). Insurance type, number of chronic conditions, having at least one baseline inpatient hospitalization, having at least one baseline ED visit, BD-I claim, anxiety, personality disorder, psychiatric medication use, oral antipsychotic medication use, and LAI initiation status were statistically significantly associated with psychiatric costs among all patients with schizophrenia (all $p < .05$).

As shown in Figure 4, early LAI initiators had lower all-cause and psychiatric healthcare costs compared with late LAI initiators in the 1-year follow-up period. Specifically, in risk-adjusted models, early LAI initiators had lower, although not statistically significant ($p = .303$), all-cause costs compared with late initiators [adjusted mean (95% CI) = $34,878 (32,759–36,7998) vs $36,241 (34,813–37,668)]. Psychiatric healthcare costs were statistically significantly lower in early initiators compared with late initiators [adjusted mean (95% CI) = $21,545 (20,355–22,734) vs $24,132 (23,330–24,933); $p < .001$].

Sensitivity analyses

Models were repeated with time to LAI initiation as a continuous variable. Results were not significant in three out of the four models (*p*-value of the time between diagnosis and LAI in the model with all-cause cost as the outcome variable: $p = .467$; psychiatric-cost: $p = .429$; all-cause hospitalization: $p = .224$; psychiatric hospitalization: $p = .043$). Using the

Table 3. All-cause and psychiatric[a] healthcare costs in the 1-year follow-up period (adjusted[b] to $2016).

	All-cause costs in post 1-year period		Total psychiatric-specific costs in post 1-year period	
	Estimate (95% CI)	*p*-value	Estimate (95% CI)	*p*-value
Age group				
18 to 34 vs 55+	−$3067 (−7023–890)	.129	$97 (−2124–2317)	.932
35 to 44 vs 55+	−$7347 (−11559–−3135)	<.001	−$1651 (−4015–713)	.171
45 to 54 vs 55+	−$4845 (−8687–−1003)	.013	−$1215 (−3372–941)	.269
Female vs Male	−$1607 (−4193–980)	.223	−$54 (−1505–1397)	.942
Insurance type				
Medicaid vs Commercial	$7919 (4490–11349)	<.001	$4761 (2837–6686)	<.001
Medicare Supplemental vs Commercial	−$11533 (−18445–−4622)	.001	−$8775 (−12654–−4896)	<.001
Charlson Comorbidity Index	$4172 (3211–5132)	<.001	$280 (−259–819)	.308
No. Chronic Conditions (HCUP)	$3393 (2479–4306)	<.001	$958 (445–1470)	<.001
Baseline hypertension (y vs n)	−$580 (−3686–2526)	.715	−$213 (−1956–1531)	.811
Baseline hyperlipidemia (y vs n)	−$1434 (−4474–1606)	.355	$759 (−947–2465)	.383
Baseline inpatient hospitalization (y vs. n)	$2325 (−524–5174)	.110	$2955 (1356–4554)	<.001
Baseline emergency department visit (y vs. n)	$6382 (3788–8975)	<.001	$2144 (689–3600)	.004
Baseline bipolar I disorder (y vs. n)	$4306 (1528–7084)	.002	$2823 (1264–4383)	<.001
Baseline major depressive disorder (y vs. n)	$177 (−2973–3327)	.912	$1427 (−341–3195)	.114
Baseline anxiety (y vs. n)	$2506 (−395–5408)	.090	$2807 (1179–4436)	<.001
Baseline personality disorder (y vs n)	$5772 (2098–9447)	.002	$2252 (190–4314)	.032
Baseline substance abuse disorder (y vs n)	−$3761 (−6467–−1056)	.006	−$1001 (−2520–517)	.196
Baseline psychiatric medication use (y vs n)	$3073 (257–5888)	.032	$1917 (337–3497)	.017
Number of baseline oral antipsychotic medication used	$4672 (3525–5820)	<.001	$3933 (3289–4577)	<.001
Early vs late LAI initiation	−$1362 (−3957–1233)	.303	−$2587 (−4043–−1131)	<.001

[a]Costs of claims with a primary diagnosis of any mental disorder (ICD-9-CM: 290.xx-311.xx; ICD-10-CM code: F01.xx-F99.xx), and costs of mental health-related treatments.
[b]Adjusted by baseline characteristics [age group, gender, insurance type, Charlson comorbidity index, no. of chronic conditions (HCUP), baseline hypertension, baseline hyperlipidemia, baseline comorbidities (including type 1 BD, MDD, anxiety, personality disorder, substance abuse disorder)], baseline inpatient hospitalization, baseline psychiatric medication use, and number of baseline oral antipsychotic medications used.

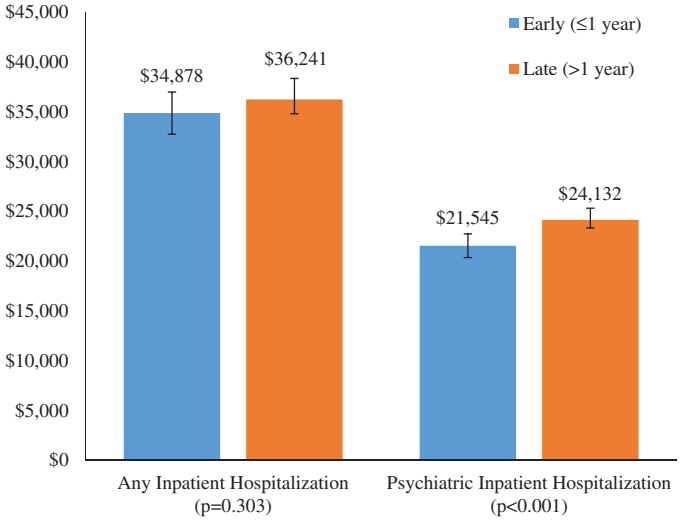

Figure 4. Risk adjusted[a] all-cause and psychiatric[b] healthcare costs in the 1-year follow-up period ($2016). Early LAI initiators had lower all-cause and psychiatric healthcare costs compared with late LAI initiators in the 1-year follow-up period.
[a]Adjusted by baseline characteristics [age group, gender, insurance type, Charlson comorbidity index, no. of chronic conditions (HCUP), baseline hypertension, baseline hyperlipidemia, baseline comorbidities (including type 1 BD, MDD, anxiety, personality disorder, substance abuse disorder)], baseline inpatient hospitalization, baseline psychiatric medication use, and number of baseline oral antipsychotic medication used.
[b]Costs of claims with a primary diagnosis of any mental disorder (ICD-9-CM: 290.xx-311.xx; ICD-10-CM code: F01.xx-F99.xx), and costs of mental health-related treatments.

quadratic term of time from diagnosis to LAI confirmed the presence of a non-linear relationship (*p*-value of the quadratic term in the model with all-cause cost as the outcome variable: $p = .005$; psychiatric cost: $p = .0003$; all-cause hospitalization: $p = .048$; psychiatric hospitalization: $p = .01$).

Discussion

This is the first, large retrospective longitudinal study to examine the effects of timing of LAI initiation in patients with new episodes of schizophrenia on hospitalization rates and healthcare costs in a real-world setting. Patients who initiated LAIs within 1 year following a new claim for schizophrenia had lower hospitalization rates and healthcare costs in the 1-year follow-up period than patients who initiated LAIs more than 1 year after such a claim, regardless of whether or not they had used oral antipsychotics prior to the LAI. Almost 32% of patients in our sample initiated a LAI within 1 year following a new episode of schizophrenia (early initiators), and 68% initiated a LAI more than 1 year after a new episode of schizophrenia (late initiators). All-cause hospitalization rates were significantly lower among early initiators, as over 22% of early initiators had at least one all-cause hospitalization compared with almost 27% of late initiators in the 1-year follow-up period. Also, psychiatric costs were significantly lower among early initiators compared to late initiators in the 1-year follow-up period (mean of $21,545 vs $24,132). The study included a wide variety of patient types, and included commercially insured, Medicare, and Medicaid patients.

Our finding that early initiation of LAIs was associated with lower all-cause hospitalization rates compared with later initiation adds to the literature on the benefits of LAIs on healthcare outcomes[26,39–41]. Previous studies have examined differences in healthcare outcomes in patients with schizophrenia treated with LAIs vs oral antipsychotics, and have shown greater benefits associated with LAIs. Specifically, compared with oral antipsychotics, LAIs have been shown to more effectively enhance medication adherence[38] and

personal and social functioning[39]; increase remission rates[39]; may provide continual neuroprotection[35]; and reduce clinical symptoms[29] and risk of relapse[42]. Also, several European studies have shown that LAIs compared with oral antipsychotics were associated with reduced risk of rehospitalization[39,43] and fewer hospitalizations[44]. For example, in a nationwide Finnish cohort study with 2588 patients hospitalized for the first time with a schizophrenia diagnosis between 2000 and 2007, analyses indicated that the risk of rehospitalization and medication discontinuation was significantly lower for patients who received LAIs compared with patients who received oral medications of the same compounds[43].

Early initiation of LAIs provided benefits associated with this formulation earlier in the course of the disease, such as increased antipsychotic adherence and reduced risk of relapse, which likely led to downstream reduced healthcare resource utilization and cost savings. In fact, several studies have concluded that schizophrenia-related costs are lower with LAIs vs oral antipsychotics[41,45–48], and a systematic review of cost-effectiveness studies deduced that LAIs are cost-effective as first-line treatment for schizophrenia[49].

Study limitations

This study has limitations. First, we do not have information about the patients' schizophrenia-related disease severity, or the length of time they had been living with the disease; we do not know if the first diagnosis (new episode) in our dataset is the true initial diagnosis. However, the new schizophrenia episode likely represents new interactions with the healthcare system, as patients were excluded if they had any medical claims for schizophrenia in the 1 year prior to their first diagnosis date found in the study ID period. Second, we arbitrarily set the distinction between early vs late LAI initiation at 1 year. We chose this threshold because it is a common one, because we believed we would have adequate data to answer the question, and because dichotomized results are easier to explain. Our sensitivity analysis suggests that the relationship between time from schizophrenia diagnosis to LAI initiation and the outcome measures is not linear, making any dichotomization potentially problematic. Further research is needed to explore whether there are inflection points at which the impact of not initiating LAI becomes more or less pronounced. Third, claims data used 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. 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; and insurance claims are often used to examine healthcare utilization, cost, and even quality of care. Fourth, we could not control for physician prescribing practices or other patient characteristics, such as underlying symptoms and socioeconomic factors. Ideally, we would like to replicate this study using a data source that has longer history, as the attrition rate in the claims dataset used for this study hindered our ability to do so. For a variety of reasons, only ~ 10% of the schizophrenia population initiates LAI treatment. Patients may resist LAIs because of stigma, fear of injections, time constraints, and costs[50–52]. Clinicians may be reluctant to prescribe LAIs due to their beliefs about side-effects, lack of evidence of superior efficacy, and lack of practical knowledge about their use[50]. To lower barriers to doctors' prescription and patients acceptance of LAIs, a substantial change in the general attitude towards LAIs as a treatment option may be required[53].

Conclusions

These results provide supportive evidence of potential benefits associated with the use of LAIs early in the course of schizophrenia treatment. Specifically, our findings indicate that early use may have beneficial effects on treatment management, adherence, relapse rates, and other outcomes, which lead to reduced hospitalization rates and healthcare costs. Future research should evaluate outcomes associated with differential treatment in first-episode schizophrenia vs new episodes that occur farther along in the disease course. Clinicians have a vital role in educating patients with schizophrenia and their caregivers about treatment options, including LAI treatment, and offering this option where appropriate in this critical period of their disease management.

Transparency

Declaration of funding

Funding for the study was received from Otsuka Pharmaceutical Development and Commercialization, Inc. and Lundbeck.

Declaration of financial/other relationships

Greene is an employee of Otsuka Pharmaceutical Development and Commercialization, Inc. Hartry is an employee of Lundbeck. Broder, Chang, Munday, and Yan are employees of PHAR, LLC, which was paid by Otsuka and Lundbeck to perform the research described in this manuscript. Peer reviewers on this manuscript have received an honorarium from CMRO for their review work, but have no other relevant financial relationships to disclose.

Acknowledgments

No assistance in the preparation of this article is to be declared.

ORCID

Ann Hartry http://orcid.org/0000-0001-8649-1311

References

[1] Weinberger DR, Harrison PJ, editors. Schizophrenia: Weinberger/Schizophrenia [Internet]. Oxford: Wiley-Blackwell; 2010 [cited 2018 Feb 9]. Available from: http://doi.wiley.com/10.1002/9781444327298.

[2] NIMH. Schizophrenia [Internet]. [cited 2018 Jan 12]. 2016 Bethesda, MD. Available from: https://www.nimh.nih.gov/health/topics/schizophrenia/index.shtml.

[3] Cloutier M, Aigbogun MS, Guerin A, et al. The economic burden of schizophrenia in the United States in 2013. J Clin Psychiatry. 2016;77:764–771.

[4] Stovall J. Bipolar disorder in adults: Epidemiology and pathogenesis [Internet]. UpToDate. 2016. Website access date 2018 Jan 12; location Waltham, MA; publisher date 2018 Feb 6. Available from: https://www.uptodate.com/contents/bipolar%C2%ADdisorder%C2%ADin%C2%ADadults%C2%ADepidemiology%C2%ADand%C2%ADpathogenesis/print?source=search_result&search=bipolar%20stovall&select%E2%80%A6.

[5] Naudet F, Maria AS, Falissard B. Antidepressant response in major depressive disorder: a meta-regression comparison of randomized controlled trials and observational studies. PLoS One. 2011;6:e20811.

[6] Lehman AF, Lieberman JA, Dixon LB, et al. Practice guideline for the treatment of patients with schizophrenia, second edition. Am J Psychiatry. 2004;161:1–56.

[7] Haas GL, Garratt LS, Sweeney JA. Delay to first antipsychotic medication in schizophrenia: impact on symptomatology and clinical course of illness. J Psychiatr Res. 1998;32:151–159.

[8] Marshall M, Rathbone J. Early intervention for psychosis. Cochrane Database Syst Rev. 2011;CD004718.

[9] de Haan L, Linszen DH, Lenior ME, et al. Duration of untreated psychosis and outcome of schizophrenia: delay in intensive psychosocial treatment versus delay in treatment with antipsychotic medication. Schizophr Bull. 2003;29:341–348.

[10] Stevens GL, Dawson G, Zummo J. Clinical benefits and impact of early use of long-acting injectable antipsychotics for schizophrenia. Early Interv Psychiatry. 2016;10:365–377.

[11] World Health Organization. Adherence to long-term therapies: evidence for action [Internet]. World Health Organization; 2003 [cited 2018 Jan 25]. Geneva 27, Switzerland. Available from: http://books.google.com/books?hl=en&lr=&id=kcYUTH8rPiwC&oi=fnd&pg=PR5&dq=%22VI+%E2%80%93+How+can+improved+adherence+be+translated+into%22+%22XIII+%E2%80%93%22+%22III+%E2%80%93+Disease-specific%22+%22VIII+%E2%80%93+Cancer+(palliative%22+%22XI+%E2%80%93%22+%22X+%E2%80%93%22+%22VII+%E2%80%93%22+%22XII+%E2%80%93%22+&ots=tz5Kir5cv_&sig=c5FxwOS1GP1PLX8P5yKo_CJzhyA.

[12] Haddad P, Brain C, Scott J. Nonadherence with antipsychotic medication in schizophrenia: challenges and management strategies. Patient Relat Outcome Meas. 2014;5:43.

[13] Lafeuille M-H, Frois C, Cloutier M, et al. Factors associated with adherence to the HEDIS quality measure in medicaid patients with schizophrenia. Am Health Drug Benefits. 2016;9:399–410.

[14] Velligan DI, Sajatovic M, Hatch A, et al. Why do psychiatric patients stop antipsychotic medication? A systematic review of reasons for nonadherence to medication in patients with serious mental illness. Patient Prefer Adherence. 2017;11:449–468.

[15] Bright CE. Measuring medication adherence in patients with schizophrenia: an integrative review. Arch Psychiatr Nurs. 2017;31:99–110.

[16] Yang J, Ko Y-H, Paik J-W, et al. Symptom severity and attitudes toward medication: impacts on adherence in outpatients with schizophrenia. Schizophr Res. 2012;134:226–231.

[17] García S, Martínez-Cengotitabengoa M, López-Zurbano S, et al. Adherence to antipsychotic medication in bipolar disorder and schizophrenic patients: a systematic review. J Clin Psychopharmacol. 2016;36:355–371.

[18] El-Mallakh P, Findlay J. Strategies to improve medication adherence in patients with schizophrenia: the role of support services. Neuropsychiatr Dis Treat. 2015;11:1077.

[19] De las Cuevas C, de Leon J, Peñate W, et al. Factors influencing adherence to psychopharmacological medications in psychiatric patients: a structural equation modeling approach. Patient Prefer Adherence. 2017;11:681–690.

[20] Pesa JA, Muser E, Montejano LB, et al. Costs and resource utilization among medicaid patients with schizophrenia treated with paliperidone palmitate or oral atypical antipsychotics. Am Health Drug Benefits . 2015;2:377–385.

[21] Bergeson JG, Kalsekar I, Jing Y, et al. Medical care costs and hospitalization in patients with bipolar disorder treated with atypical antipsychotics. Am Health Drug Benefits. 2012;5:379–386.

[22] Greenberg PE, Fournier A-A, Sisitsky T, et al. The economic burden of adults with major depressive disorder in the United States (2005 and 2010). J Clin Psychiatry. 2015;76:155–162.

[23] Lafeuille M-H, Gravel J, Lefebvre P, et al. Patterns of relapse and associated cost burden in schizophrenia patients receiving atypical antipsychotics. J Med Econ. 2013;16:1290–1299.

[24] Greene M, Yan T, Chang E, et al. Medication adherence and discontinuation of long-acting injectable versus oral antipsychotics in patients with schizophrenia or bipolar disorder. J Med Econ. 2018;21:127–134.

[25] Yan T, Greene M, Chang E, et al. All-cause hospitalization and associated costs in patients with schizophrenia or bipolar disorder initiating long-acting injectable antipsychotics. Curr Med Res Opin. 2018;34:41–47.

[26] Kishimoto T, Robenzadeh A, Leucht C, et al. Long-acting injectable vs oral antipsychotics for relapse prevention in schizophrenia: a meta-analysis of randomized trials. Schizophr Bull. 2014;40:192–213.

[27] Francey SM, Nelson B, Thompson A, et al. Who needs antipsychotic medication in the earliest stages of psychosis? A reconsideration of benefits, risks, neurobiology and ethics in the era of early intervention. Schizophr Res. 2010;119:1–10.

[28] Girardi P, Del Casale A, Rapinesi C, et al. Predictive factors of overall functioning improvement in patients with chronic schizophrenia and schizoaffective disorder treated with paliperidone palmitate and aripiprazole monohydrate. Hum Psychopharmacol Clin Exp. 2018;33:e2658.

[29] Parellada E, Andrezina R, Milanova V, et al. Patients in the early phases of schizophrenia and schizoaffective disorders effectively treated with risperidone long-acting injectable. J Psychopharmacol. 2005;19:5–14.

[30] Emsley R, Chiliza B, Asmal L, et al. Long-acting injectable antipsychotics in early psychosis: a literature review. Early Interv Psychiatry. 2013;7:247–254.

[31] Stahl SM. Long-acting injectable antipsychotics: shall the last be first? CNS Spectr. 2014;19:3–5.

[32] Kim B, Lee S-H, Yang YK, et al. Long-acting injectable antipsychotics for first-episode schizophrenia: the pros and cons. Schizophr Res Treat. 2012;2012:1–8.

[33] Taylor M, Ng KYB. Should long-acting (depot) antipsychotics be used in early schizophrenia? A systematic review. Aust N Z J Psychiatry. 2013;47:624–630.

[34] Brugnoli R, Rapinesi C, Kotzalidis GD, et al. Model of Management (Mo.Ma) for the patient with schizophrenia: crisis control, maintenance, relapse prevention, and recovery with long-acting injectable antipsychotics (LAIs). Riv Psichiatr. 2016;51:47–59.

[35] Bartzokis G, Lu PH, Amar CP, et al. Long acting injection versus oral risperidone in first-episode schizophrenia: differential impact on white matter myelination trajectory. J Chronic Dis. 2011;132:35–41.

[36] Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40:373–383.

[37] Chi M, Lee C, Wu S. The prevalence of chronic conditions and medical expenditures of the elderly by chronic condition indicator (CCI). Arch Gerontol Geriatr. 2011;52:284–289.

[38] Weiden PJ, Schooler NR, Weedon JC, et al. A randomized controlled trial of long-acting injectable risperidone vs continuation on oral atypical antipsychotics for first-episode schizophrenia patients: initial adherence outcome. J Clin Psychiatry. 2009;70:1397–1406.

[39] Barrio P, Batalla A, Castellví P, et al. Effectiveness of long-acting injectable risperidone versus oral antipsychotics in the treatment of recent-onset schizophrenia: a case–control study. Int Clin Psychopharmacol. 2013;28:164–170.

[40] Kane JM, Kishimoto T, Correll CU. The comparative effectiveness of long-acting injectable vs. oral antipsychotic medications in the prevention of relapse: a case study in CER in psychiatry. J Clin Epidemiol. 2013;66:S37–S41.

[41] Lin J, Wong B, Offord S, et al. 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.

[42] Kim B, Lee S-H, Choi TK, et al. Effectiveness of risperidone long-acting injection in first-episode schizophrenia: in naturalistic setting. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32: 1231–1235.

[43] Tiihonen J, Haukka J, Taylor M, et al. A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. Am J Psychiatry. 2011;168:603–609.

[44] Willis M, Svensson M, Löthgren M, et al. The impact on schizophrenia-related hospital utilization and costs of switching to long-acting risperidone injections in Sweden. Eur J Health Econ. 2010;11:585–594.

[45] Offord S, Wong B, Mirski D, et al. Healthcare resource usage of schizophrenia patients initiating long-acting injectable antipsychotics vs oral. J Med Econ. 2013;16:231–239.

[46] Kane JM, Sanchez R, Zhao J, et al. Hospitalisation rates in patients switched from oral anti-psychotics to aripiprazole once-monthly for the management of schizophrenia. J Med Econ. 2013;16: 917–925.

[47] Crivera C, DeSouza C, Kozma CM, et al. Resource utilization in patients with schizophrenia who initiated risperidone long-acting therapy: results from the Schizophrenia Outcomes Utilization Relapse and Clinical Evaluation (SOURCE). BMC Psychiatry. 2011; 11:168.

[48] Bera R, Offord S, Zubek D, et al. Impact on healthcare resource usage and costs among Medicaid-insured schizophrenia patients after initiation of treatment with long-acting injectable antipsychotics. J Med Econ. 2013;16:522–528.

[49] Achilla E, McCrone P. The cost effectiveness of long-acting/extended-release antipsychotics for the treatment of schizophrenia. Appl Health Econ Health Policy. 2013;11:95–106.

[50] Correll CU, Citrome L, Haddad PM, et al. The use of long-acting injectable antipsychotics in schizophrenia: evaluating the evidence. J Clin Psychiatry. 2016;77:1–24.

[51] Kirschner M, Theodoridou A, Fusar-Poli P, et al. Patients' and clinicians' attitude towards long-acting depot antipsychotics in subjects with a first episode of psychosis. Ther Adv Psychopharmacol. 2013;3:89–99.

[52] Potkin S, Bera R, Zubek D, et al. Patient and prescriber perspectives on long-acting injectable (LAI) antipsychotics and analysis of in-office discussion regarding LAI treatment for schizophrenia. BMC Psychiatry. 2013;13:261.

[53] Sacchetti E, Grunze H, Leucht S, et al. Long-acting injection antipsychotic medications in the management of schizophrenia. Evid-Based Psychiatr Care. 2015;1:27–36.