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ORIGINAL RESEARCH

Medication adherence and discontinuation of long-acting injectable versus oral antipsychotics in patients with schizophrenia or bipolar disorder

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ABSTRACT

Aims: To examine medication adherence and discontinuation in two separate groups of patients with schizophrenia or bipolar disorder (BD), who began receiving a long-acting injectable antipsychotic (LAI) versus those who changed to a different oral antipsychotic monotherapy.

Materials and methods: The Truven Health Analytics MarketScan Multi-State Medicaid claims database was used to identify patients with schizophrenia; Truven Health Analytics MarketScan Commercial and Medicaid claims databases were used to identify patients with BD. The analyses included adult patients (≥18 years) who either began receiving an LAI (no prior LAI therapy) or changed to a different oral antipsychotic (monotherapy). The first day of initiating an LAI or changing to a new oral antipsychotic was the index date. Linear and Cox regression models were conducted to estimate medication adherence (proportion of days covered [PDC]) and time to medication discontinuation (continuous medication gap ≥60 days), respectively. Models adjusted for patient demographic and clinical characteristics, baseline medication use, and baseline ED or hospitalizations.

Results: Patients with schizophrenia ($N = 5638$) who began receiving LAIs had better medication adherence (5% higher adjusted mean adherence) during the 1 year post-index period and were 20% less likely to discontinue their medication during the entire follow-up period than patients who changed to a different oral antipsychotic monotherapy, adjusting for differences between LAI users and oral users. Similarly, patients with BD ($N = 11{,}344$) who began receiving LAIs also had 5% better medication adherence and were 19% less likely to discontinue their medication than those using oral antipsychotics.

Limitations: Clinical differences unmeasurable in this database may have been responsible for the choice of LAI versus oral antipsychotics, and these differences may be responsible for some of the adherence advantages observed.

Conclusions: This real-world study suggests that patients with schizophrenia or BD who began receiving LAIs had better medication adherence and lower discontinuation risk than those who changed to a different oral antipsychotic monotherapy.

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Medication adherence; medication discontinuation; schizophrenia; bipolar disorder; long-acting injectable antipsychotics; oral antipsychotics

Introduction

Schizophrenia and bipolar disorder (BD) are chronic, relapsing psychiatric disorders affecting 1.1% (2.7 million) and 2.6% (5.7 million), respectively, of the adult population in the United States[1,2]. Pharmacologic treatment is the cornerstone of management for both diseases[2–4]. Medication nonadherence is a significant problem in many chronic conditions[5] and may be one of the most challenging aspect of treating patients with schizophrenia and BD[5,6]. Rates of nonadherence to schizophrenia medication range from 34% to 81%, depending on the method of assessment and metric used, with many studies reporting rates of around 50%[7–13]. BD medication nonadherence rates range from 20% to 60%, with an average of 40%[11].

Multiple strategies have been used to improve adherence, including family and/or clinician support and education, text message and phone reminders, motivational interviewing, and financial incentives. Pharmacological interventions, such as switching to a different oral antipsychotic or switching to a long-acting injectable (LAI) antipsychotic, have also been advocated[14–16]. LAI formulations of antipsychotics have been developed in part to improve treatment adherence. With administration schedules ranging from biweekly to every 3 months, LAIs may improve outcomes in patients with schizophrenia[17–23]. Antipsychotic medications have also been increasingly used either as monotherapy or as adjunctive therapy in BD[24,25] and may be particularly beneficial in nonadherent patients[26]. Among LAIs with US Food and Drug Administration (FDA) approval for treatment of schizophrenia (aripiprazole monohydrate [Abilify Maintena[1]; AOM 400], fluphenazine decanoate, haloperidol decanoate, olanzapine pamoate, paliperidone palmitate 4 week [Invega Sustenna[2]], risperidone microspheres, aripiprazole lauroxil [Aristada[3]], and

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paliperidone palmitate 12 week [Invega Trinza[4]]), only AOM 400 and risperidone LAI are approved for maintenance treatment of bipolar I disorder, although others are used off-label[27].

Current treatment guidelines for schizophrenia recommend that clinicians consider LAIs, not only in patients who are inadequately adherent to pharmacological therapy[28–32], but also for patients who prefer such treatment[33]. However, clinicians may not offer patients choices about treatment[32] and, when they do, some patients resist the recommendation of LAIs[14]. Studies of adherence may be best conducted in a real-world setting, as medication use is more closely monitored in randomized control trials RCTs than is practical on a wide scale, and RCTs frequently last only weeks to months, too short providing meaningful information about drugs that must be taken indefinitely[32]. There have been limited real-world studies examining adherence between LAI and oral antipsychotics, and these studies have not included some of the most recently approved LAIs such as AOM 400.

Using real-world data, we conducted two separate retrospective cohort analyses – one focusing on patients with schizophrenia and the other on patients with BD – to compare differences in medication adherence and discontinuation between those who initiated an LAI and those who changed from one oral antipsychotic monotherapy to another.

Methods

Data source and study design

To identify patients with schizophrenia, we used administrative claims data from the Truven Health Analytics MarketScan Multi-State Medicaid claims database. This database includes demographic and clinical information, inpatient and outpatient utilization data, and outpatient prescription data for 40 million Medicaid enrollees from multiple geographically dispersed states in the US. To identify patients with BD, we analyzed claims data from both Truven MarketScan Medicaid and commercial databases. The MarketScan commercial database includes medical and pharmacy claims for approximately 65 million individuals and their dependents who are covered through employer-sponsored private health insurance plans. Most patients with schizophrenia are insured through the Medicaid or Medicare programs[34–36], and those who are not may differ systematically (e.g. be less severely ill). We attempted to identify commercially insured patients with schizophrenia including those with Medicare supplemental insurance in order to examine this group but found only nine qualifying individuals. We therefore confined the analysis to schizophrenic individuals with Medicaid coverage. To ensure complete medication claims histories, patients with Medicare dual eligibility and those without mental health coverage were excluded. The data used for both analyses were from 1 January 2012 through 30 June 2015. All data was compliant with the Health Insurance Portability and Accountability Act (HIPAA) of 1996. Institutional review board approval was not required.

Sample selection

Among patients with at least one inpatient or two outpatient claims for schizophrenic disorders (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM]: 295.xx) at any time during the entire study period, we identified two mutually exclusive cohorts. The LAI cohort comprised patients ("LAI users") with schizophrenia and at least one claim for available LAIs (aripiprazole monohydrate [Abilify Maintena; AOM 400], fluphenazine decanoate, haloperidol decanoate, olanzapine pamoate, paliperidone palmitate 4 week [Invega Sustenna], or risperidone microspheres) during the identification (ID) period (1 January 2013 through 30 June 2014). Two currently marketed LAIs (aripiprazole lauroxil [Aristada] and paliperidone palmitate 12 week [Invega Trinza]) were approved after the study end date and were not included. The index date was defined as the earliest occurrence (the first date) of a claim for one of the LAI therapies of interest during the ID period. The LAI observed on the index date was defined as the index therapy. Patients were allowed to have claims for non-index LAI therapies in the year prior to index (baseline period). Among the remaining patients (those with no LAI use), the oral cohort was defined as patients ("oral users") who changed from one oral antipsychotic therapy to another oral antipsychotic monotherapy during the ID period. The index date for this cohort was the earliest date of the new oral antipsychotic prescription. All patients were required to have continuous enrollment for 1 year before and 1 year after the index date. Patients were followed for at least 1 year and until the end of enrollment or study end, whichever occurred first. For all patients, the first diagnosis of schizophrenia was required to be before the index date.

We applied analogous patient selection and cohort identification criteria to identify a group of patients with BD (ICD-9-CM: 296.0x, 296.1x, 296.4x, 296.6x, 296.7x, 296.8x) who either initiated an LAI or changed to an oral monotherapy.

Outcome measures

Medication adherence was measured by proportion of days covered (PDC) in the 1 year immediately post-index. PDC was calculated as the number of available days of index therapy divided by 365[37]. For oral antipsychotics, the days' supply as reported on the prescription claim was used to calculate the PDC. For LAIs, given that the days' supply field is often unavailable or of questionable accuracy, the days' supply on each claim was set to the minimum time between injections per the labeled dosing schedule for the given drug[38]. For example, since AOM 400 has a monthly dosing interval, the days' supply was set to 30. Nonadherence was defined as PDC less than 0.80. Medication discontinuation was defined as either a switch or a gap of $\geq$60 days in available days' supply[34] during the entire follow-up. A switch was defined as a claim for a non-index therapy within 60 days after the index therapy discontinuation date.

Baseline measures

Baseline variables that were potentially related to illness severity and adherence behavior were examined using data from the 1-year pre-index baseline period. These included: sociodemographics (age, sex, and race), Charlson Comorbidity Index (CCI)[39,40], number of chronic condition indicators[41], somatic comorbidities (obesity, diabetes mellitus, hyperlipidemia, and hypertension), somatic medication use (anti-diabetic medications, lipid-lowering medications, and anti-hypertensive medications), psychiatric medication use (antidepressants, anti-anxiety medications, and sedatives or hypnotics), and any baseline inpatient hospitalizations or emergency department (ED) visits. We reported the presence of claims for other psychiatric conditions. Unlike in our patient identification algorithm (which required one inpatient or two outpatient claims for the target condition), we identified patients as having depression, anxiety, personality disorder, substance abuse disorder, BD (in the group of patients with schizophrenia), and schizophrenia (in patients with BD) by the presence of a single code for the relevant condition.

Statistical analysis

Descriptive analyses were performed to assess differences between LAI and oral cohorts across baseline covariates. Chi-square tests were used to assess differences in proportions of categorical variables, and two sample *t*-tests were used to test differences in means of continuous variables. A linear regression model was conducted to examine the association between the oral and LAI cohorts and medication adherence, adjusted for baseline covariates, including age, gender, race (White vs. non-White), CCI[39,40], number of chronic condition indicators[41], any baseline inpatient hospitalizations or ED visits, depression, anxiety, BD (schizophrenia for the group of patients with BD), and any baseline psychiatric or somatic medication use. A Kaplan–Meier curve and a Cox regression were conducted to estimate time to and risks of medication discontinuation, respectively, adjusting for the baseline covariates mentioned above. All data transformations and statistical analyses were performed using SAS version 9.4.

Results

Patient selection and baseline characteristics

Of the 79,826 patients with schizophrenia identified from the Truven Medicaid database, 5638 met the study selection criteria. The final analytic sample for patients with schizophrenia included 2861 (50.7%) LAI users and 2777 (49.3%) oral users. Of the 381,369 patients with BD identified from the Truven Commercial and Medicaid databases, 11,344 met the study selection criteria. The final analytic sample for patients with BD included 1672 (14.7%) LAI users and 9672 (85.3%) oral users (Figure 1). Follow-up was similar in both groups: schizophrenia mean (SD) 633.6 (150.7) days for LAI, 634.9 (158.0) for oral; BD 627.4 (154.7) for LAI, 639.5 (159.6) for oral. The difference was statistically significant for BD ($p = .043$) but not for schizophrenia ($p = .737$).

Among patients with schizophrenia, statistically significant differences in several sociodemographic and clinical characteristics were observed between LAI and oral users. LAI users

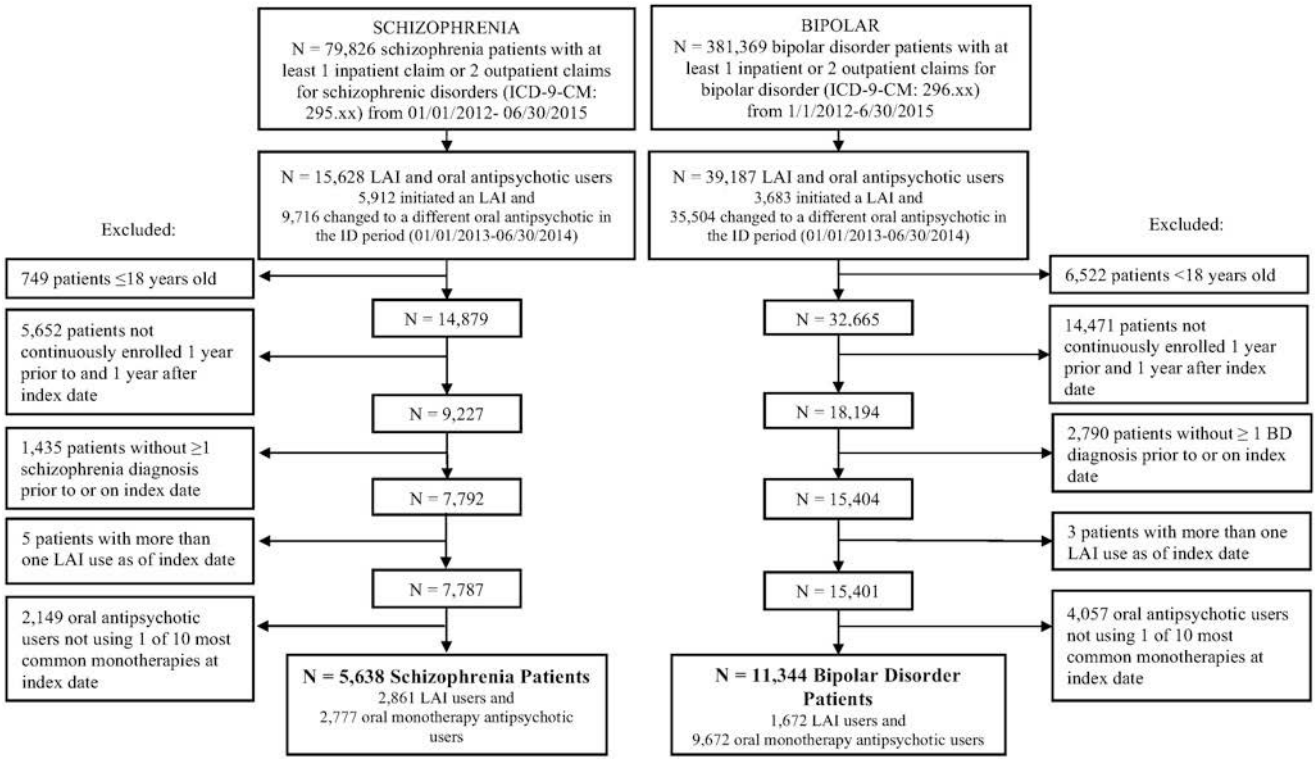

Figure 1. Patient identification.

Table 1. Patient characteristics.

	Schizophrenia N = 5638		p value	Bipolar disorder N = 11,344		p value
	LAIs[a] N = 2861; 50.7%	Orals[b] N = 2777; 49.3%		LAIs[c] N = 1672; 14.7%	Orals[d] N = 9672; 85.3%	
Demographics						
Age in years, mean (SD)	39.9 (13.2)	42.0 (13.1)	<.001	36.1 (13.3)	39.1 (13.4)	<.001
Female, *n* (%)	1,238 (43.3)	1,526 (55.0)	<.001	1,392 (83.3)	4,068 (42.1)	<.001
Medicaid enrollees, *n* (%)	2,861 (100%)	2,777 (100%)		842 (50.4)	6,570 (67.9)	<.001
Race, *n* (%)						
White	851 (29.7)	1,149 (41.4)	<.001	–	–	
African American	1,650 (57.7)	1,146 (41.3)		–	–	
Other	360 (12.6)	482 (17.4)		–	–	
Comorbidities						
Charlson Comorbidity Index, mean (SD)	1.1 (1.9)	1.7 (2.3)	<.001	1.2 (1.8)	1.1 (1.8)	.062
No. chronic conditions, mean (SD)	3.5 (2.3)	4.4 (2.4)	<.001	4.0 (2.3)	4.0 (2.2)	.706
Psychiatric comorbidities, *n* (%)	2,190 (76.5)	2,397 (86.3)	<.001	1,531 (91.6)	8,063 (83.4)	.004
Depression	1,300 (45.4)	1,641 (59.1)	<.001	918 (54.9)	5,569 (57.6)	.041
Anxiety	1,019 (35.6)	1,352 (48.7)	<.001	830 (49.6)	5,403 (55.9)	<.001
Personality disorder	399 (13.9)	395 (14.2)	.784	346 (20.7)	1,074 (11.1)	<.001
Substance abuse disorders	1,505 (52.6)	1,574 (56.7)	.002	1,005 (60.1)	4,504 (46.6)	<.001
Bipolar disorders	1,028 (35.9)	1,250 (45.0)	<.001	–	–	
Schizophrenia	–	–		1,127 (67.4)	1,613 (16.7)	<.001
Somatic comorbidities, *n* (%)	1618 (56.6)	1,808 (65.1)	<.001	948 (56.7)	4,959 (51.3)	<.001
Baseline[e] medication and healthcare service use						
Use of any oral antipsychotic medication, *n* (%)	2,277 (79.6)	2,777 (100.0)	–	1,465 (87.6)	9,672 (100.0)	–
Any use of selected psychiatric medications, *n* (%)	1,895 (66.2)	2,342 (84.3)	<.001	1,406 (84.1)	9,091 (94.0)	<.001
Somatic medications, *n* (%)	1,243 (43.4)	1,510 (54.4)	<.001	770 (46.1)	4,706 (48.7)	.001
Any inpatient hospitalization or ED visit, *n* (%)	1,910 (66.8)	2,058 (74.1)	<.001	1,363 (81.5)	6,634 (68.6)	<.001

[a]Frequency of index LAI therapy in patients with schizophrenia: 1235 paliperidone; 741 haloperidol; 387 risperidone; 258 aripiprazole; 186 fluphenazine; 54 olanzapine.
[b]Frequency of index oral therapy in patients with schizophrenia: 495 quetiapine; 470 risperidone,; 365 olanzapine; 320 lurasidone; 270 aripiprazole; 225 ziprasidone; 194 haloperidol; 110 paliperdone; 328 other.
[c]Frequency of index LAI therapy in patients with bipolar disorder: 741 paliperidone; 324 haloperidol; 251 risperidone; 224 aripiprazole; 97 fluphenazine; 35 olanzapine.
[d]Frequency of index oral therapy in patients with bipolar disorder: 2098 quetiapine; 1643 aripiprazole; 1584 lurasidone; 1310 risperidone; 1103 olanzapine; 935 ziprasidone; 441 asenapine; 271 haloperidol; 287 other.
[e]One year prior to the index date.

were younger than oral users (mean [SD] age: 39.9 [13.2] vs. 42.0 [13.1]; $p < .001$). A higher percentage of LAI users were male and African American when compared to oral users. Compared to oral users, LAI users had a significantly lower mean CCI score and a lower mean number of chronic conditions, lower psychiatric and somatic comorbid disease rates, and less ED or hospitalization utilization during the baseline period (Table 1).

Among patients with BD, LAI users were younger than oral users (mean [SD] 36.1 [13.3] years vs. 39.1 [13.4] years; $p < .001$). A higher percentage of LAI users were female and had commercial insurance than oral users. LAI users also had higher rates of personality disorder, substance abuse disorders, schizophrenia, somatic comorbid disease, and ED or hospitalization use than oral users (Table 1).

Unadjusted medication adherence rate and time to discontinuation

Table 2 shows the descriptive outcomes during the 1 year post-index period. For the group of patients with schizophrenia, LAI users had significantly better medication adherence (PDC ≥0.8: 33.9% vs. 25.5%, $p < .001$; unadjusted PDC mean: 0.55 vs. 0.50, $p < .001$) and a significantly lower discontinuation rate (63.2% vs. 72.0%, $p < .001$) than oral users. LAI users also had a significantly longer time to medication discontinuation than the oral users during the entire follow-up period. The median time to discontinue index LAI was 196 days compared with 123 days for oral users ($p < .001$) (Figure 2).

Similar results were found for the group of patients with BD. Compared with oral users, LAI users had significantly better medication adherence (PDC ≥0.8: 30.9% vs. 21.5%, $p < .001$; unadjusted PDC mean: 0.51 vs.0.45, $p < .001$) and a significantly lower discontinuation rate (67.9% vs. 77.4%, $p < .001$) during the 1 year post-index period (Table 2). The median time to discontinue index for LAI users was 149 days compared to 99 days for oral users ($p < .001$) (Figure 3).

Adjusted medication adherence rate and risk of discontinuation

Among patients with schizophrenia, linear regression and Cox regression models controlling for all differences in measured covariates (listed previously in baseline measures) confirmed that the adjusted mean PDC remained higher in LAI users than in oral users (LAI users vs. oral users: 0.55 vs. 0.50, $p < .001$), and oral users had a higher risk of discontinuing their index treatments than LAI users (hazard ratio [HR]: 1.20, $p < .001$) (Table 3).

Similarly, among patients with BD, the adjusted mean PDC was 5% higher in LAI users than in oral users (0.50 vs. 0.45, $p < .001$). Oral users had 19% higher risk of discontinuing treatment than LAI users (HR: 1.19, $p < .001$) (Table 3).

Table 2. Unadjusted results: proportion of days covered (PDC) and medication discontinuation during the 1 year follow-up period.

	Schizophrenia		*p* value	Bipolar disorder		*p* value
	LAIs $N = 2,861$; 50.7%	Orals $N = 2,777$; 49.3%		LAIs $N = 1,672$; 14.7%	Orals $N = 9,672$; 85.3%	
PDC, mean (SD)	0.552 (0.333)	0.499 (0.440)	<.001	0.506 (0.341)	0.452 (0.410)	<.001
Medication adherence rate (PDC ≥0.8), *n* (%)	970 (33.9)	709 (25.5)	<.001	516 (30.9)	2,084 (21.5)	<.001
Duration of index treatment without a gap ≥60 days, mean (SD) days	281.8 (251.9)	234.9 (245.4)	<.001	250.9 (240.3)	202.0 (218.6)	<.001
Discontinuation rate, *n* (%)	1,809 (63.2)	2,000 (72.0)	<.001	1,136 (67.9)	7,484 (77.4)	<.001

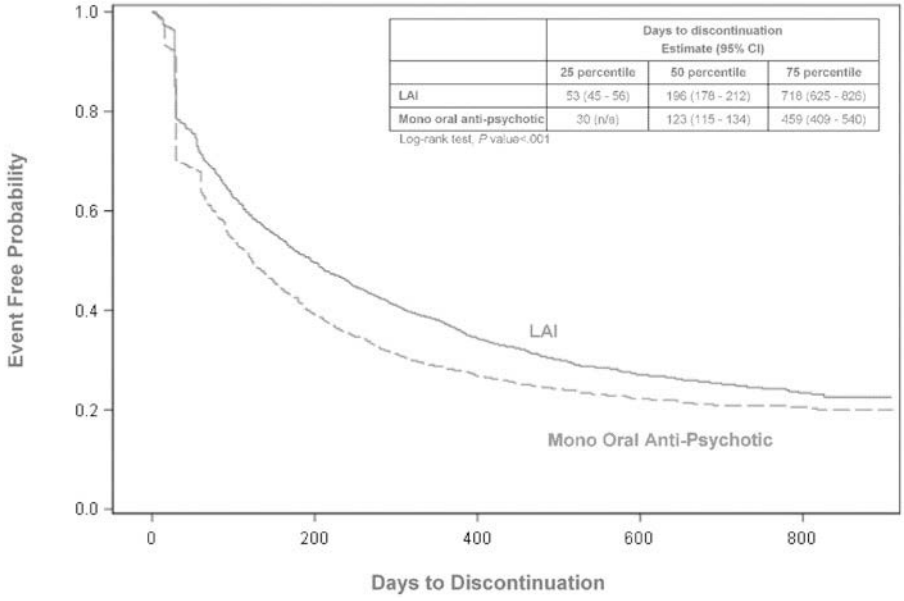

Figure 2. Time to discontinuation of index treatment (schizophrenia).

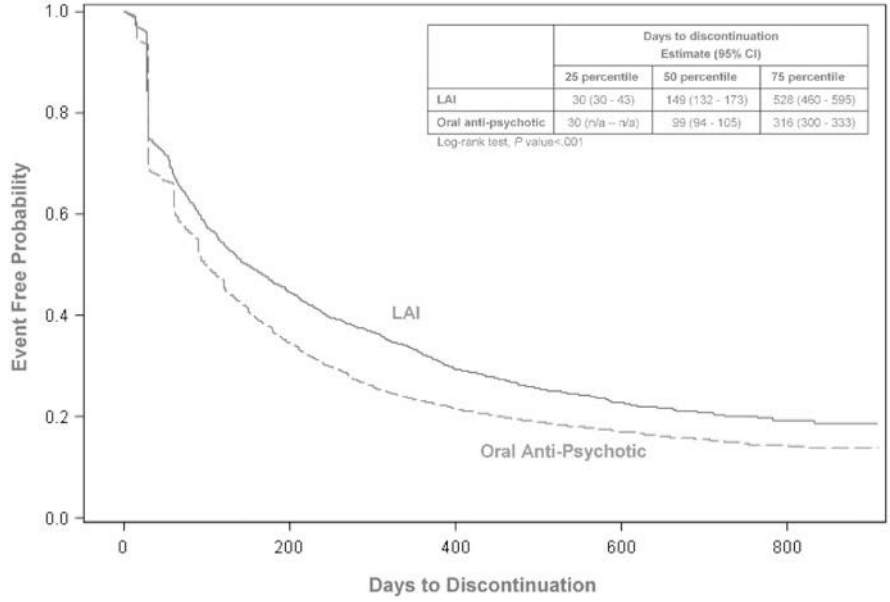

Figure 3. Time to discontinuation of index treatment (bipolar disorder).

Discussion

In this large retrospective study, medication adherence and discontinuation were compared between patients who initiated an LAI and those who changed their oral antipsychotic monotherapy in two groups: patients with schizophrenia and patients with BD. Patients with schizophrenia initiating LAIs had better medication adherence (8% higher medication adherence rate and 5% higher adjusted mean adherence) during the 1 year post-index period, had 73 day longer median time to medication discontinuation, and were 20%

Table 3. Multivariate[a] results: risk of discontinuation and adjusted medication adherence (PDC) estimates.

Mono oral antipsychotic (Ref: LAI)	Risk of Discontinuation of Index Treatment in Follow-up Period[b]		Index Treatment PDC During the 1 year Follow-up Period[c]	
	HR (95% CI)	*p* value	Estimate (95% CI)	*p* value
Schizophrenia	1.20 (1.13–1.28)	<.001	−0.054 (−0.075 to −0.033)[d]	<.001
Bipolar disorder	1.19 (1.12–1.28)	<.001	−0.045 (−0.068 to −0.022)[e]	<.001

[a]Adjusted for age groups, gender, race (White vs. non-White), Charlson Comorbidity Index, number of chronic conditions, any baseline inpatient hospitalization or ED visit, depression, anxiety, BD (schizophrenia for the group of patients with BD), any baseline psychiatric medication use, and any baseline somatic medication use.
[b]Cox regression model.
[c]General linear regression model.
[d]Adjusted mean (95% CI) PDC: LAIs 0.553 (0.539–0.567); orals 0.499 (0.484–0.513).
[e]Adjusted mean (95% CI) PDC: LAIs 0.498 (0.477–0.519); orals 0.453 (0.445–0.461).

less likely to discontinue their medication during the entire follow-up period (≥365 days) than patients who changed to different oral antipsychotic monotherapy, even when controlling for differences between LAI initiators and oral users. Similarly, patients with BD initiating LAIs also had better medication adherence (9% higher medication adherence rate and 5% higher adjusted mean adherence), had a 50 day longer median time to medication discontinuation, and were 19% less likely to discontinue their medication than oral-treated patients.

Most of the existing observational studies in the US that compared medication adherence and discontinuation between LAI and oral users in either schizophrenia or BD are limited to within a 1 year period[19,34] or have a relatively small sample size of patients[42,43], but our findings are consistent with prior observational studies[19,34,43,44]. For example, using claims, Marcus *et al.* reported that 48.2% of patients with schizophrenia treated with LAIs and 32.3% of oral users had PDC ≥0.8 during the 6 months post hospital discharge[34]. A recent study of schizophrenia patients in Medicaid found 27.2% of LAI patients were adherent to index medication at 12 months compared to 24.6% of oral users[19]. In 40 pairs of matched patients, Brnabic and colleagues[42] estimated that patients with schizophrenia treated with LAIs had a 67% reduction in risk of discontinuation compared to oral-treated patients over a 1 year period. Many more studies have examined outcomes associated with LAI use than have directly compared adherence between LAI and oral therapy. Pesa *et al.* found that once monthly paliperidone was more favorable at reducing hospitalization amongst patients with schizophrenia compared to oral antipsychotics[45]. A meta-analysis of randomized trials[46] found a statistically significant reduction in relapse among patients with schizophrenia treated with LAI compared to oral formulations. Using a subset of five of the included studies (three completed before 1980), the authors found a non-statistically-significant relative risk for nonadherence of 0.76 (95% CI 0.37 to 1.56) for LAIs. Literature on the use of LAIs to improve adherence in BD is even more limited. In a 2016 systematic review of adherence to antipsychotics, García *et al.* identified 13 studies that included BD patients, two of which commented on the use of first generation LAIs to improve adherence, neither reporting original research[11].

Despite the known clinical and practical benefits of LAIs over oral antipsychotics, they are still used less in the United States than in many other countries[47]. Our study provides further evidence that using LAIs could be one part of a larger, multipronged approach to combating the problem of poor adherence in patients with schizophrenia or BD. Negative attitudes towards LAIs may interfere with their use[32,48]. Clinicians may be reluctant to prescribe LAIs for a variety of reasons, including the mistaken beliefs that LAIs are associated with more adverse effects[32], their perceived "permanence", and even ethical grounds. Patients may resist LAIs because of stigma, fear or hesitation about injections, time constraints, and costs[14]. Other barriers, such as a lack of community nurses to administer injections and healthcare payers' reluctance to cover LAIs unless there is clear documentation of nonadherence may also exist.

Innovative approaches to increase patient engagement and train more psychiatrists and their staff in the use of LAIs may help facilitate their use in different settings. For the group of patients with schizophrenia, our study shows that LAI initiators were younger and had a lower comorbidity disease burden than oral-treated patients. Therefore, strategies promoting LAIs should also be tailored to a variety of individuals who are nonadherent to their medication, including those who may be earlier in the course of their disease but healthier overall, as well as those who may be suffering repeated relapses late in disease.

This study had limitations. First, variables not contained in the claims databases, such as attitudes of clinicians and patients to LAIs or disease severity, may have been responsible for the choice of LAI vs. oral antipsychotics, and these differences may be responsible for some of the adherence advantage observed (or conversely, may have attenuated the advantage of LAIs). Second, schizophrenia and BD diagnoses were identified from healthcare claims coded for reimbursement. Misclassification, diagnostic uncertainty, or coding errors were possible. Third, claims do not provide perfect information about medication use. A prescription fill does not mean the medication was used, or that it was taken as prescribed. Further, if the intended dosing interval differs from the labeled one (for example an LAI intentionally given every 3 weeks rather than the labeled 2 weeks), our estimates of adherence would be inaccurate. Nevertheless, health insurance claims data remain a valuable source of information, as they constitute a valid, large sample of patient characteristics and outcomes in a real-world setting. Fourth, the states included in the database are not individually identifiable, and the database

does not include information on patient race/ethnicity or geographic region. Fifth, about 20% of the patients with schizophrenia who were treated with LAIs and more than 12% of the patients with BD in the LAI cohort did not use any oral antipsychotic medications during the study baseline. Since LAIs are not typically the initial medication used, these patients may have been prescribed oral therapy but did not fill (or refill) their prescription – possibly a more severely ill group. Alternatively, they could represent a group of patients started primarily on LAIs, but these two possibilities could not be distinguished in the current study. Sixth, we examined adherence to index therapy, rather than any therapy – discontinuation of index therapy did not mean lack of treatment, as some patients switched to an alternative antipsychotic. Seventh, not all statistically significant results are clinically meaningful. Finally, the results for schizophrenia may not be generalizable to non-Medicaid populations.

Conclusions

Medication adherence and discontinuation are important determinants of medication effectiveness, as the benefits of even highly effective medications will be achieved only if patients adhere to prescribed treatment regimens. By including more recently approved LAIs and analyzing large insurance claims databases, our study contributes to the real-world evidence that LAIs are more effective than oral antipsychotics in improving medication adherence and reducing medication discontinuation among patients with schizophrenia. Patients with BD demonstrated similar benefits from the use of LAIs. LAIs play a potentially important role in real-world clinical practice. Future real-world studies are warranted to further delineate potential advantages of one LAI versus another in improving patient outcomes.

Transparency

Declaration of funding

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Author contributions: All authors met the *ICMJE* criteria for authorship, including contributing to study concept and design, interpretation of the data, and to the drafting and critical review of the manuscript. E.C. further contributed to the analysis of the data. This manuscript has been read and approved by all authors.

Declaration of financial/other relationships

M.G. has disclosed that he is an employee of Otsuka Pharmaceutical Development and Commercialization Inc. T.Y., M.S.B. and E.C. have disclosed that they are employees of Partnership for Health Analytic Research LLC. A.H. and M.T. have disclosed that they are employees of Lundbeck.

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Notes

1. Otsuka America Pharmaceuticals, Inc., Rockville, MD
2. Janssen Pharmaceuticals, Inc., Titusville, NJ
3. Alkermes, Inc., Waltham, MA
4. Janssen Pharmaceuticals, Inc., Titusville, NJ

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