



# Adherence, Persistence, Readmissions, and Costs in Medicaid Members with Schizophrenia or Schizoaffective Disorder Initiating Paliperidone Palmitate Versus Switching Oral Antipsychotics: A Real-World Retrospective Investigation

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## ABSTRACT

**Introduction:** Long-acting injectable antipsychotic agents have been suggested to improve adherence and patient outcomes in schizophrenia or schizoaffective disorder. The purpose of this study was to assess medication use patterns (i.e., medication adherence, persistence), hospital and emergency department readmissions, and total direct medical costs of Oklahoma Medicaid members with schizophrenia or schizoaffective disorder switching from an oral antipsychotic (OAP) to once-monthly paliperidone palmitate (PP1M) or to another OAP (OAP-switch).

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**Methods:** A historical cohort analysis was conducted from 1 January 2016 to 31 December 2020 among adults aged  $\geq 18$  and  $\leq 64$  years with schizophrenia or schizoaffective disorder who were previously treated with an OAP. The first claim for PP1M or a new OAP defined the study index date. Members who transitioned from PP1M to 3-month formulation (PP3M) were included (i.e., PP1M/PP3M). Proportion of days covered (PDC), 45-day treatment gaps, 30-day readmissions to hospitals or emergency department, and total direct medical costs were assessed using multivariable, machine-learning least absolute shrinkage, and selection operator (Lasso) regressions controlling for numerous demographic, clinical, mental health, and provider characteristics.

**Results:** Among 295 Medicaid members meeting full inclusion criteria, 183 involved PP1M/PP3Ms (44 PP1M cases transitioned to PP3M) and 112 involved an OAP-switch. The multivariable-adjusted odds of readmission were significantly associated with a 45-day treatment gap ( $p < 0.05$ ) and non-adherence (i.e., PDC < 80%) ( $p < 0.05$ ). Relative to PP1M/PP3Ms, the multivariable analyses also indicated that OAP-switch was associated with an 18.5% lower PDC, 92.3% higher number of 45-day treatment gaps, and an approximately 90% higher odds of all-cause 30-day readmission ( $p < 0.05$ ). The adjusted pre- to post-index change in cost was approximately 49% lower for OAP-switches

versus PP1M/PP3Ms ( $p < 0.001$ ), although unadjusted post-index costs did not differ between groups ( $p = 0.440$ ).

**Conclusion:** This real-world investigation of adult Medicaid members with schizophrenia or schizoaffective disorder observed improved adherence and persistence with fewer readmissions with PP1M/PP3Ms versus OAP-switches.

**Keywords:** Adherence; Costs; Machine learning; Medication switches; Oral antipsychotics; Paliperidone palmitate; Persistence; Readmissions; Schizoaffective disorder; Schizophrenia

### Key Summary Points

#### *Why carry out this study?*

Persons with schizophrenia (SCZ) or schizoaffective disorder (SCD) often require switches in therapy. Compared with oral antipsychotic medications (OAP), long-acting injectable antipsychotic medications may be associated with improved adherence and persistence and reductions in hospitalizations, readmissions, and costs.

This study assessed medication adherence, persistence, readmissions, and total comprehensive direct medical costs of Oklahoma Medicaid members with SCZ or SCD previously treated with an OAP who switched to once-monthly paliperidone palmitate (PP1M) or another OAP.

#### *What was learned from the study?*

Results from multivariable, machine-learning least absolute shrinkage, and selection operator (Lasso) regression observed significantly improved adjusted adherence and persistence, fewer readmissions, and a greater change in total costs for members switching to PP1M compared with those switching to another OAP.

The presence of any 45-day gap in medication treatment was independently associated with a 2.7 times adjusted higher odds of hospital or emergency department readmission, whereas adherence (defined as 80% or greater proportion of days covered) was associated with a 65% lower adjusted odds of readmission.

Targeted and supportive interventions are needed to minimize poor adherence and persistence and improve outcomes in this vulnerable population.

## INTRODUCTION

Schizophrenia (SCZ) is a severe psychiatric disorder with a substantial health, social, occupational, and economic burden [1]. In the USA, prevalence of SCZ is estimated to be between 0.25% and 0.64% [2, 3] and is one of the top 20 causes of disability [4]. SCZ is associated with an increased risk of substance abuse, suicide, and mortality compared with the general population [1, 5]. Schizoaffective disorder (SCD) is a psychiatric disorder characterized by mixed symptoms of SCZ and mood disorders [6]. The estimated lifetime prevalence of SCD is 0.3%, and the presence of SCD is associated with higher rates of hospitalization, suicide, and substance abuse compared with SCZ [6]. Cloutier et al. [7] estimated that the total annual economic burden of SCZ in the USA was \$150 billion, with 24% involving direct patient care related to inpatient services, medications, and outpatient services [7]. Inpatient and emergency department (ED) care is estimated to account for 10% of total healthcare costs [7].

Antipsychotic agents are used in the management of acute episodes of SCZ and SCD, and in the continued management following recovery to prevent relapse [1, 8]. The American Psychological Association (APA) practice guidelines recommend treatment for patients to include initiating antipsychotic medication, continuing treatment once symptoms improve (e.g., adherence), and maintaining consistent

treatment over time (e.g., persistence) [1]. Numerous oral antipsychotic agents (OAPs) have been approved specifically for use in SCZ and SCD [6, 9, 10]. Newer second-generation long-acting injectable antipsychotic agents (LAIs) have been introduced and are recommended by the APA in cases involving known non-adherence, or if substantial uncertainty surrounds medication-taking behavior [1]. Despite positive clinical outcomes of continued therapy to mitigate SCZ or SCD relapse, treatment non-adherence occurs in up to 50% of patients [11]. Several factors may contribute to non-adherence or poor persistence in SCZ and SCD, with management interventions often requiring a switch in OAP therapeutic agents or initiating LAIs [1, 12, 13].

Kane et al. [12] noted that switching among OAPs or initiating an LAI was an advocated clinical approach to address non-adherence, while Haddad et al. [13] stated that a trial of LAIs might assist clinicians to ascertain if potential treatment failure in SCZ could be due to either non-adherence or treatment resistance. APA guidelines recommend that patients with SCZ who have a history of poor or uncertain adherence receive LAI therapy [1]. A meta-analysis conducted by Lin et al. [14], which included Medicaid and claims-based analyses, reported that the utilization of LAIs was associated with an improved odds of medication adherence compared with OAPs. LAIs were also associated with a lower odds for hospitalization and fewer admissions to hospitals or EDs [14]. LAIs may also be associated with improved persistence relative to OAPs [15]. In a 2021 meta-analysis of real-world studies, the relative risk of treatment discontinuation was lower with an LAI formulation of risperidone versus several OAPs [15].

Paliperidone palmitate is an LAI with a 1-month formulation (PP1M) approved by the US Food and Drug Administration (FDA) for both SCZ and SCD [16], and with 3-month (PP3M) and 6-month (PP6M) formulations approved specifically for SCZ [17, 18]. Research indicates that PP1M use is associated with a lower odds of hospital admission and potentially lower costs compared with OAPs in SCZ [19–22]. Building upon previous studies, a

continued need exists to assess the association between PP1M/PP3M use on adherence, persistence, readmissions, and costs, particularly in applying more robust and extensive multivariable models to control for potential confounders of outcomes. Incorporating machine-learning algorithms, the objective of this study was to assess medication use patterns (i.e., medication adherence, persistence), readmissions, and total direct medical costs of Oklahoma Medicaid members with SCZ or SCD previously treated with an OAP and switching to PP1M or another OAP (OAP-switch).

## METHODS

This retrospective study utilized an historical cohort of comprehensive, transaction-level medical and pharmacy Oklahoma Medicaid administrative claims data from 1 January 2016 to 31 December 2019. More specifically, these data represented more than 750,000 Oklahoma Medicaid members and included information on demographics (e.g., age, sex, race, metro/urban residence), pharmacy claims (e.g., drug, date of transaction, quantity filled, days' supply, prescriber, reimbursement amount), and medical claims (e.g., diagnoses, inpatient/outpatient/ED visits, long-term care, reimbursement amount). This study was defined as exempt by the Office of Human Research Participant Protection (institutional review board #12942) at the University of Oklahoma Health Sciences Center.

The study population comprised adult Medicaid members  $\geq 18$  and  $\leq 64$  years of age with one or more inpatient or two or more outpatient claims involving relevant SCZ or SCD diagnoses [based on International Classification of Diseases, Ninth or Tenth Revision, Clinical Modification (ICD-9-CM, ICD-10-CM) [23, 24] codes for SCZ (295.XX, F20.XX) or SCD (297.5, F25.9)] plus two or more prescription claims for an OAP within a 6-month period before switching to another OAP (for qualifying medications, see Supplementary Material Appendix S1). The study's index date was defined as the initial PP1M prescription fill (following pre-index OAP use) or an OAP

monotherapy switch (with the “OAP-switch” defined by the first claim of a new OAP following a pre-index OAP and also requiring two or more paid prescription claims for the new OAP within 60 days after the first claim). Inclusion criteria also required continuous Medicaid eligibility for a minimum of 12 months pre-index and at least 12 months post-index. Exclusion criteria included any use of clozapine across the study’s timeframe, any concomitant LAI use, dual Medicaid and Medicare eligibility (i.e., due to limited data availability), or any healthcare coverage within the Indian Health Service (i.e., also due to limited data availability). No index medication could be utilized within 6 months prior to the index date to ensure that members were naïve to an index medication.

Two comparative cohorts were defined via the index medication category as: (1) PP1M treatment initiation following pre-index OAP use (e.g., a switch from an OAP to PP1M defined as “PP1M initiation”) and (2) switching to a different OAP following pre-index OAP use (i.e., defined as “OAP-switch”). Members of the PP1M cohort were permitted to transition to PP3M; therefore, the PP1M initiation cohort also included those that extended treatment in the PP1M/PP3M group. A paid prescription claim for PP1M or PP3M required prior authorization from Oklahoma Medicaid throughout the study timeframe, and prior authorization criteria of a PP1M or PP3M were in congruence with FDA-approved indications for use [16, 17]. Thus, consistent with medical practice standards and medication labeling, Medicaid members could transition to PP3M only if they were adequately treated with PP1M. The rationale for the choice of comparators of PP1M/PP3M and OAP-switch was based on guideline recommendations that patients who are non-adherent to OAP therapy be switched to an LAI [1], though real-world clinical observations have indicated that many non-adherent cases are switched to another OAP rather than initiating treatment with an LAI [25]. The study’s focus on paliperidone palmitate is, in part, due to its uniquely different indication within the therapeutic class—paliperidone is the only long-acting injectable antipsychotic (LAI) with a current indication that also includes schizoaffective

disorder [16]. Overall, paliperidone palmitate (PP1M) as a focal LAI has received substantial attention by the clinical and scientific community, summarized across 25 studies within the meta-analysis conducted by Lin et al. [14]. The study’s outcomes of medication use patterns included adherence [defined via a continuous measure of proportion of days covered (PDC)] and persistence (defined as the continuous or count number of 45-day treatment gaps). Of note, PDC remains a recommended approach to measuring adherence, and is calculated as the number of days covered by the medication divided by the number of days in the study period following the index date until the end of follow-up (i.e., the number of days in the measurement period) [26]. Additional study outcomes included any all-cause 30-day readmission to the ED or hospital and costs, defined as total comprehensive direct medical costs from the perspective of a Medicaid payer (i.e., complete medical, ambulatory, inpatient, ED, procedure, pharmacy, home health, and other administrative claims).

Independent variables of interest assessed during the pre-index period included age, sex, race, residence (i.e., urban, micropolitan/rural), SCZ diagnosis type (i.e., paranoid, disorganized, catatonic, undifferentiated/simple, residual, other), SCD diagnosis, presence of mental health comorbidities [i.e., bipolar disorder, major depressive disorder, and post-traumatic stress disorder (PTSD)], Deyo–Charlson Comorbidity Index (D-CCI) [27], and the number of years since initial SCZ or SCD diagnosis. Clinical independent variables included the use of an OAP, pre-index ED or inpatient admission [28], pre-index total comprehensive direct medical costs [29], provider type (i.e., primary care/generalist, specialist physician including psychiatrist, nurse practitioner, physician assistant), and index year. Importantly, the analysis also included control for potential differences in post-index follow-up time (i.e., among members with eligibility and treatment extending beyond 12 months). As a predictor variable, a PDC  $\geq$  80% was used as a dichotomous marker for adherence, which is commonly used in real-world evidence research and has been validated in predicting hospital

admissions associated with SCZ [30]. The presence of any 45-day treatment gap as a predictor variable was used as a dichotomous measure for persistence. Owing to inherent collinearity that is present between the measures (i.e., correlation between variables), the  $PDC \geq 80\%$  and presence of any 45-day treatment gap variables were incorporated into separate regression models for the outcomes of SCZ or SCD resource utilization (i.e., readmissions) and costs. A complete list of regression variables is presented in Supplementary Material Appendix S2.

Bivariable statistical comparisons between PP1M/PP3M and OAP-switch cohorts were conducted using independent-group *t*-tests or chi-squared tests, as appropriate. A multivariable, machine-learning least absolute shrinkage and selection operator (Lasso) regression was specified for the main inferential analysis, providing a validated and robust statistical framework to analyze high-dimensional models with numerous predictors [31–34]. In more detail, a cross-fit partialing-out Lasso was employed via a: (1) linear regression with a Napierian logarithmic-transformed outcome used for the continuous measure of PDC; (2) Poisson regression for the count number of 45-day gaps; (3) logistic regression for the presence of any 30-day readmission; and (4) linear regression for the Napierian logarithmic-transformed total direct comprehensive medical costs from the perspective of a Medicaid payer [29, 31–35]. All Lasso regressions were specified with Lasso penalty parameter optimization via a plugin iterative formula, repeat sample splitting ten times, tenfold within each split for cross-fitting, and Eicker–Huber–White heteroscedasticity-robust standard error estimation [31–34, 36–38]. The use of Napierian logarithms was warranted owing to the skewed nature of both PDC and cost outcomes, and was required to ensure minimum variance unbiased estimators (MVUE); these transformations were validated through extensive residual diagnostics [35]. Outcomes were reported as exponentiated beta estimates ( $\exp(\beta_{\text{estimate}})$ ) for PDC and costs, incidence rate ratios (IRR) for the number of 45-day treatment gaps, and odds ratios (OR) for readmissions based on linear, Poisson, or logistic regressions, respectively, with associated

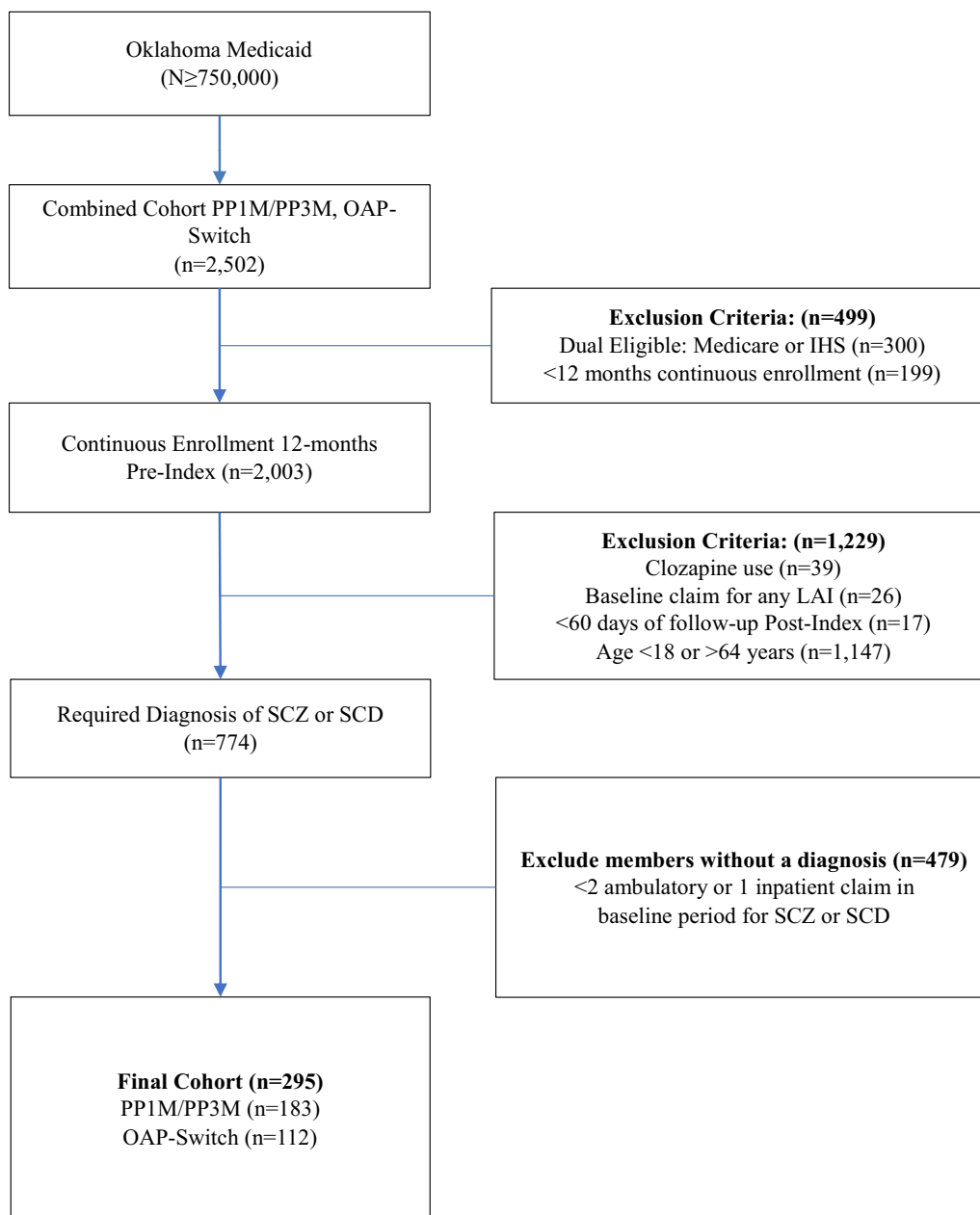
95% confidence intervals (CIs) [29, 35]. Of note, the coefficient estimates obtained from log-transformed continuous outcomes may also be interpreted as semi-elasticities, and a log–log transformation of both continuous outcome and continuous predictor may be interpreted as a constant or full elasticity [35]. Given the potential for differences that may have occurred owing to interruptions in care associated with the coronavirus disease 2019 (COVID-19) pandemic, sensitivity analyses were also conducted to evaluate the index year of 2019; explicit control for this potential confounder was retained within all Lasso regression analyses, irrespective of this sensitivity analysis. All analyses were performed using SAS version 9.4 (Cary, NC) or Stata MP version 17.0 (College Station, TX).

## RESULTS

### Descriptives

Overall, 295 Medicaid members met full inclusion criteria; 62.0% ( $n = 183$ ) were in the PP1M/PP3M cohort and 38.0% ( $n = 112$ ) in the OAP-switch cohort (Fig. 1). Twenty-four percent (44 of 183) of members who received PP1M transitioned to PP3M treatment during the post-index period. The average duration of post-index follow-up was  $1.5 \pm 0.8$  years.

The average age across both cohorts was  $39.7 \pm 12.6$  years; 48.1% of the population was female, and 22.7% was African American or Black (Table 1). The D-CCI had an overall mean and standard deviation of  $1.13 \pm 1.84$ . There were no significant differences observed in the proportions of SCZ or SCD members in the PP1M/PP3M versus OAP-switch cohorts ( $p \geq 0.05$ ). The OAP-switch cohort was generally older ( $42.0 \pm 13.2$  versus  $38.4 \pm 12.0$  years), had a higher proportion of females (55.4% versus 44.8%), and had a higher proportion of white race (74.1% versus 61.8%) compared with the PP1M/PP3M cohort ( $p < 0.05$  for all comparisons). In addition, OAP-switch members had higher D-CCI scores than the PP1M/PP3M cohort ( $1.5 \pm 2.1$  versus  $0.9 \pm 1.6$ ,  $p < 0.01$ ), though neither score was necessarily indicative



**Fig. 1** Attrition diagram of study inclusion and exclusion criteria. *PP1M* paliperidone palmitate every month, *PP3M* paliperidone palmitate every 3 months, *OAP* oral antipsychotic,

*IHS* Indian Health Service, *LAI* long-acting injectable antipsychotic, *SCZ* schizophrenia, *SCD* schizoaffective disorder

of numerous other chronic conditions [27]. To illustrate, OAP-switch members had higher proportions of comorbid bipolar disorder (50.0% versus 35.0%) and comorbid PTSD (61.6% versus 42.1%) than the PP1M/PP3M cohort ( $p < 0.05$ ). Concerning baseline OAP medication use, 28.0% were prescribed

risperidone overall, while 22.3% were prescribed olanzapine. OAP-switch members were associated with a higher proportion of baseline quetiapine (23.2% versus 13.9%,  $p < 0.05$ ) than the PP1M/PP3M cohort. An index year of 2017 was more common in the OAP-switch cohort

**Table 1** Baseline descriptive statistics of adult Medicaid members ( $\geq 18$  years of age) with schizophrenia or schizoaffective disorder according to once-monthly paliperidone palmitate (PP1M) switch or oral antipsychotic (OAP) switch treatment type

	PP1M/PP3M cohort ( <i>n</i> = 183)	OAP-switch cohort ( <i>n</i> = 112)	Overall ( <i>n</i> = 295)
<b>Demographics</b>			
Age in years (mean $\pm$ SD)	38.4 $\pm$ 12.0*	42.0 $\pm$ 13.2*	39.7 $\pm$ 12.6
Female (%)	44.8%*	55.4%*	48.1%
<b>Race (%)</b>			
White (%)	61.8%*	74.1%*	66.4%
African American or Black (%)	26.8%*	16.1%*	22.7%
Other (%)	11.5%	9.8%	10.9%
Residence, micropolitan or rural (%)	37.6%	41.3%	38.5%
<b>Prescriber characteristics</b>			
Physician assistant or nurse practitioner (%)	26.2%	26.8%	26.4%
Specialist (%)	38.3%	36.6%	37.6%
<b>Deyo–Charlson Comorbidity Index (mean <math>\pm</math> SD)</b>			
Zero (%)	59.0%*	44.6%*	53.6%
1–4 (%)	35.5%*	44.6%*	39.0%
5–9 (%)	$\leq 5.0\%^b$	10.7%*	7.1%
10 or above (%)	$\leq 5.0\%^b$	$\leq 5.0\%^b$	$\leq 5.0\%^b$
<b>Mental health characteristics</b>			
Comorbid bipolar disorder (%)	35.0%**	50.0%**	40.7%
Comorbid PTSD (%)	11.5%	15.2%	12.9%
Comorbid major depressive disorder (%)	42.1%***	61.6%***	49.5%
Baseline risperidone (%)	29.8%	25.0%	28.0%
Baseline olanzapine (%)	23.4%	20.5%	22.3%
Baseline quetiapine (%)	13.9%*	23.2%*	17.4%
Baseline aripiprazole (%)	11.4%	14.3% <sup>b</sup>	12.5%
Baseline ziprasidone (%)	$\leq 5.0\%^b$	$\leq 5.0\%^b$	7.8%
Baseline lurasidone (%)	$\leq 5.0\%^b$	$\leq 5.0\%^b$	5.4%
Baseline asenapine (%)	$\leq 5.0\%^b$	$\leq 5.0\%^b$	$\leq 5.0\%^b$
Baseline iloperidone (%)	$\leq 5.0\%^b$	$\leq 5.0\%^b$	$\leq 5.0\%^b$
<b>Schizophrenia or SCD characteristics</b>			
SCD (%)	69.4%	74.1%	71.2%

**Table 1** continued

	PP1M/PP3M cohort ( <i>n</i> = 183)	OAP-switch cohort ( <i>n</i> = 112)	Overall ( <i>n</i> = 295)
Paranoid-type schizophrenia (%)	21.9%	25.0%	23.1%
Disorganized-type schizophrenia (%)	≤ 5.0%	≤ 5.0%	≤ 5.0%
Catatonic-type schizophrenia (%)	≤ 5.0% <sup>b</sup>	≤ 5.0% <sup>b</sup>	≤ 5.0% <sup>b</sup>
Undifferentiated/simple-type schizophrenia (%)	≤ 5.0% <sup>b</sup>	≤ 5.0% <sup>b</sup>	≤ 5.0% <sup>b</sup>
Residual-type schizophrenia (%)	≤ 5.0% <sup>b</sup>	≤ 5.0% <sup>b</sup>	≤ 5.0% <sup>b</sup>
Other or unknown-type schizophrenia (%)	≤ 5.0% <sup>b</sup>	≤ 5.0% <sup>b</sup>	≤ 5.0% <sup>b</sup>
Years since first schizophrenia or SCD diagnosis (%)	5.8 ± 4.1	6.1 ± 4.4	5.9 ± 4.2
Resource utilization and costs (pre-index)			
Total direct medical costs (USD 2020) (mean ± SD)	\$16,125 ± 19,151***	\$31,634 ± 32,534***	\$22,013 ± 26,143
Any 30-day admission (%)	60.0%	66.9%	62.4%
ED/inpatient cost <sup>a</sup>	\$5,393 ± 9,236*	\$9,918 ± 16,117*	\$ 3,946 ± 9,942
Pharmacy cost	\$4,082 ± 10,384	\$3,394 ± 4,641	\$3,821 ± 8,660
Index year			
2017 (%)	33.9%*	49.1%*	39.7%
2018 (%)	34.4%*	25.9%*	31.1%
2019 (%)	31.7%*	25.0%*	29.2%

*SD* standard deviation, *ED* emergency department, *OAP* oral antipsychotic, *PP1M* paliperidone palmitate every month, *PP3M* paliperidone palmitate every 3 months, *PTSD* post-traumatic stress disorder, *SCD* schizoaffective disorder, *USD* US dollar

\* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$  between groups via independent groups *t*-test or chi-squared

<sup>a</sup>Average total direct medical costs (comprehensive including pharmacy, ambulatory, and acute care) when Medicaid member incurred one or more ED visit or inpatient hospitalization

<sup>b</sup>Indicates variable falls within the Centers for Medicare and Medicaid Services (CMS) Cell Size Suppression Policy, which limits direct sample size reporting to more than ten cases [50]

than in the PP1M/PP3M cohort (49.1% versus 33.9%,  $p = 0.01$ ).

Unadjusted results indicated that adherence was low irrespective of treatment cohort, with an average PDC of  $66.7 \pm 29.8$  overall and some 48.5% reaching a PDC of 80% or greater (Table 2); no significant difference between cohorts was observed in unadjusted measures of adherence ( $p \geq 0.05$ ). Concerning persistence,

OAP-switches had a higher proportion of unadjusted post-index 45-day treatment gaps compared with PP1M/PP3M members (24.1% versus 18.7%,  $p = 0.037$ ). Of the members incurring a 45-day treatment gap, OAP-switches had a higher proportion of two or more gaps (9.0% versus 2.1%,  $p = 0.008$ ). The OAP-switch cohort had higher unadjusted pre-index total direct medical costs relative to the PP1M/PP3M



**Table 2** Unadjusted post-index results of medication treatment characteristics, resource utilization, costs, and duration of follow-up

	PP1M/PP3M cohort (n = 183)	OAP-switch cohort (n = 112)	Overall (n = 295)
Treatment characteristics			
Proportion of days covered (PDC) ≥ 80%	50.3%	45.5%	48.5%
Proportion of days covered (PDC) (mean ± SD)	68.6 ± 27.5	63.6 ± 33.0	66.7 ± 29.8
Presence of any OAP or PP1M/PP3M 45-day treatment gap (%)	18.7%*	24.1%*	21.1%
No 45-day gaps (%)	81.3%*	75.8%*	78.9%
One 45-day gap (%)	16.5%*	15.2%*	15.9%
Two or more 45-day gaps (%)	≤ 5.0% <sup>b</sup>	9.0%*	5.2%
PP1M transition to PP3M (%)	24.0%	–	–
Resource utilization and costs			
Total direct medical costs (USD 2020) (mean ± SD)	\$48,998 ± 43,791	\$52,962 ± 65,276	\$50,503 ± 52,911
ED/inpatient cost <sup>a</sup>	\$4846 ± 15,478**	\$12,882 ± 17,533**	\$4,394 ± 13,026
Pharmacy cost	\$32,185 ± 24,323***	\$9,040 ± 14,559***	\$23,398 ± 23,935
Any post-index 30-day readmission (%)	33.3%*	42.0%*	36.6%
Duration of follow-up, in years (mean ± SD)	1.4 ± 0.8	1.6 ± 1.1	1.5 ± 0.8

SD standard deviation, ED emergency department, OAP oral antipsychotic, PP1M paliperidone palmitate every month, PP3M paliperidone palmitate every 3 months, USD US dollar

\**p* < 0.05, \*\**p* < 0.01, \*\*\**p* < 0.001 between groups via independent groups *t*-test or chi-squared

<sup>a</sup> Average total direct medical costs (comprehensive including pharmacy, ambulatory, and acute care) when Medicaid member incurred one or more ED visit or inpatient hospitalization

<sup>b</sup> Indicates variable falls within the Centers for Medicare and Medicaid Services (CMS) Cell Size Suppression Policy, which limits direct sample size reporting to more than ten cases [50]

cohort (\$31,634 ± 32,534 versus \$16,125 ± 19,151, *p* < 0.001), although post-index costs were similar between groups (\$52,963 ± 65,276 versus \$48,998 ± 43,791, *p* = 0.440). Lastly, the OAP-switch cohort had a higher proportion of any 30-day post-index readmission compared with the PP1M/PP3M cohort (42.0% versus 33.3%, *p* = 0.042).

### Multivariable, Machine-Learning Lasso Regression Analyses

The multivariable Lasso regression analysis for adherence, persistence, resource utilization, and cost outcomes explicitly controlled for potential differences across demographics, clinical characteristics, provider types, index years, total number of years since initial SCZ or SCD diagnosis, and duration of follow-up (Table 3). Concerning adherence outcomes, OAP-switches were significantly associated with a lower adjusted PDC and a higher adjusted incidence

**Table 3** Multivariable, machine-learning Lasso regression<sup>a</sup> for outcomes of adherence, persistence, readmissions, and costs

	Medication adherence outcome	Medication persistence outcome	Resource utilization outcomes		Cost outcomes	
	Proportion of days covered (PDC) <sup>b</sup> exp( $\beta_{estimate}$ ) (95% CI)	Number of 45-day treatment gaps <sup>c</sup> IRR (95% CI)	Any 30-day readmission <sup>d,e</sup> (PDC as a predictor) Odds ratio (95% CI)	Any 30-day readmission <sup>d,e</sup> (treatment gap as a predictor) Odds ratio (95% CI)	Total direct medical costs <sup>b</sup> (PDC as a predictor) exp( $\beta_{estimate}$ ) (95% CI)	Total direct medical costs <sup>b</sup> (treatment gap as a predictor) exp( $\beta_{estimate}$ ) (95% CI)
OAPs (versus PP1M/PP3M)	0.815* (0.678, 0.979)	1.923** (1.234, 2.299)	1.874* (1.031, 3.411)	1.911* (1.071, 3.410)	0.511*** (0.400, 0.653)	0.501*** (-0.393, -0.693)
Pre-index ED or inpatient hospitalization	0.865 (0.720, 1.035)	1.599* (1.051, 2.433)	4.863*** (2.641, 8.958)	5.227*** (2.728, 10.015)	(Not reported, though included within Lasso parameter selection)	(Not reported, though included within Lasso parameter selection)
Pre-index costs (log-transformed) <sup>f</sup>	-	-	-	-	1.306*** (1.198, 1.413)	1.312*** (1.021, 1.418)
PDC ( $\geq 80\%$ )	-	-	0.341** (0.180, 0.644)	-	1.252* (1.020, 1.537)	-
Presence of 45-day treatment gap	-	-	-	2.717** (1.407, 5.247)	-	1.072 (-0.841, 1.366)

CI confidence interval, ED emergency department, IRR incidence rate ratio, Lasso least absolute shrinkage and selection operator, OAP oral antipsychotic agent, PDC proportion of days covered, PP1M paliperidone palmitate every month, PP3M paliperidone palmitate every 3 months

<sup>a</sup>All Lasso regressions specified with Lasso penalty parameter optimization via a plugin iterative formula, repeat sample splitting ten times, tenfold within each split for cross-fitting, and Eiker–Huber–White heteroscedasticity-robust standard error estimation. In addition to oral antipsychotic agents or PP1M/PP3M, pre-index emergency department or inpatient hospitalization, and proportion of days covered or presence of 45-day treatment gap, the lasso explicitly controlled the following independent variables: age; sex; race; place of residence (i.e., urban, micropolitan/rural); schizophrenia diagnosis type (i.e., paranoid, disorganized, catatonic, undifferentiated/simple, residual, other); schizoaffective disorder diagnosis; provider type (i.e., primary care, specialist physician/psychiatrist, nurse practitioner, physician assistant); presence of mental health comorbid conditions to include bipolar disorder, major depressive disorder, and post-traumatic stress disorder; Deyo–Charlson Comorbidity Index; index year; number of years since initial schizophrenia or schizoaffective disorder diagnosis; and duration of follow-up

<sup>b</sup>Cross-fit partialing-out Lasso linear regression with log-transformed outcome to yield semi-elasticities (exponentiated beta estimate, exp( $\beta_{estimate}$ )). Additionally, this Lasso explicitly controlled for pre-index total direct medical costs (i.e., comprehensive costs including pharmacy, ambulatory, and acute care) from the Medicaid payer perspective

<sup>c</sup>Cross-fit partialing-out Lasso Poisson regression to yield incidence rate ratios

<sup>d</sup>Cross-fit partialing-out Lasso logistic regression to yield odds ratios

<sup>e</sup>Includes readmission to hospital or ED

<sup>f</sup>Log-transformed (Napierian/natural log, base 2, ln) outcome and predictor yields full/constant elasticities

\* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$

–, variable omitted/not included in the model

of 45-day treatment gaps relative to PP1M/PP3M. More specifically, an OAP-switch was associated with a 18.5% lower PDC measure [exp( $\beta_{estimate}$ ) = 0.815, CI 0.678–0.979,

$p = 0.030$ ] and a 92.3% higher number of 45-day treatment gaps (IRR 1.923, CI 1.234–2.299,  $p = 0.004$ ). Irrespective of treatment cohort, the presence of a pre-index ED

visit or inpatient admission was associated with 59.9% more 45-day treatment gaps compared with members without any pre-index visit or admission (IRR 1.599, CI 1.051–2.433,  $p = 0.028$ ).

When controlling for a PDC  $\geq 80\%$  as a dichotomous measure of adherence in the multivariable analysis of SCZ or SCD resource utilization, OAP-switches were significantly associated with an 87.4% higher adjusted odds of any 30-day readmission relative to PP1M/PP3Ms (OR 1.874, CI 1.031–3.411,  $p = 0.030$ ). Additionally, a PDC  $\geq 80\%$  was associated with a 65.9% lower adjusted odds of any 30-day post-index readmission (OR 0.341, CI 0.180–0.644,  $p = 0.001$ ). When controlling for the presence of any 45-day treatment gap as a dichotomous measure of persistence, OAP-switches were associated with a 91.1% higher adjusted odds of any readmission (OR 1.911, CI 1.071–3.410,  $p = 0.028$ ), whereas the presence of any 45-day treatment gap was associated with 2.717 times higher adjusted odds of any readmission overall (CI 1.407–5.247,  $p = 0.003$ ), irrespective of treatment cohort. Across both regressions, a pre-index admission was a significant predictor of any 30-day readmission, with an adjusted odds ratio of 4.863 when controlling for PDC  $\geq 80\%$  (CI 4.641–8.958,  $p < 0.001$ ) and 5.227 when controlling for the presence of any 45-day treatment gap as a predictor (CI 2.728–10.015,  $p < 0.001$ ).

The multivariable analysis of total comprehensive direct medical costs indicated that OAP-switches were associated with an adjusted pre- to post-index change of approximately –49% relative to PP1M/PP3M ( $\exp[\beta_{\text{estimate, PDC} \geq 80\% \text{ as a predictor}}] = 0.511$  and  $\exp[\beta_{\text{estimate, treatment gap as a predictor}}] = 0.501$ ,  $p < 0.001$ ) (Table 3). Overall, a 25.2% increase in adjusted post-index costs was associated with PDC  $\geq 80\%$  ( $\exp[\beta_{\text{estimate}}] = 1.252$ , CI 1.020–1.537,  $p = 0.032$ ), whereas the presence of any 45-day treatment gap was not associated with a pre- versus post-index change in costs ( $\exp[\beta_{\text{estimate}}] = 1.072$ , CI –0.841 to 1.366,  $p = 0.576$ ). For each 1% increase in pre-index costs, a significant 0.31% increase was observed in adjusted post-index costs ( $\exp[\beta_{\text{estimate, PDC} \geq 80\% \text{ as a predictor}}] = 1.306$  and  $\exp[\beta_{\text{estimate, treatment gap as a predictor}}] = 1.312$ ,

$p < 0.001$ ), reflecting a full or constant cost elasticity [29].

Comprehensively, across all multivariable analyses, sensitivity analyses surrounding COVID-19 era cases did not suggest that any differences were present ( $p \geq 0.05$ ). Again, via the Lasso regression analyses, the overall analysis retained explicit control for any potential changes that may have occurred.

## DISCUSSION

The current historical cohort analysis of Oklahoma Medicaid members assessed medication use patterns, resource utilization/readmissions, and total comprehensive direct medical costs among 295 members with SCZ or SCD who switched to a PP1M from a pre-index OAP or switched to a different OAP medication. Machine-learning, multivariable Lasso regression analyses indicated that Medicaid members who underwent an OAP-switch had significantly lower adjusted medication adherence (i.e., 18.5% lower PDC measure) and lower persistence (i.e., 92.3% higher number of 45-day treatment gaps) compared with those who initiated PP1M/PP3Ms ( $p < 0.05$ ). The multivariable analysis also indicated that OAP-switches were associated with an 87.4% or 91.1% higher adjusted odds of any readmission controlling for PDC  $\geq 80\%$  or the presence of any 45-day treatment gap, respectively ( $p < 0.05$ ). The multivariable-adjusted change in costs from pre- to post-index was approximately 49% lower for OAP-switch ( $p < 0.05$ ), although the total overall unadjusted post-index costs did not differ between the PP1M/PP3M versus OAP-switch cohorts ( $p = 0.440$ ). While treatment adherence defined by PDC  $\geq 80\%$  was associated with a 25.2% higher pre- to post-index change in adjusted costs ( $p = 0.032$ ), fewer than half achieved a threshold of PCD  $\geq 80\%$  overall.

The current study builds on previous work in several important ways, with a key strength afforded by utilizing high-dimensional, machine-learning, multivariable statistical approaches to incorporate multiple predictors in a robust manner. Therein, Lasso regression

analyses simultaneously controlled for numerous demographics, SCZ diagnosis types, providers, mental health comorbidities, clinical case mixes, longitudinal attributes, and health system characteristics, and included robust standard error estimations to ensure that potential violations required for statistical inference were mitigated. Lasso regression, overall, is a particularly useful machine-learning approach to estimate coefficients under conditions of small sample inference in the presence of numerous and extensive covariate control [39]. An additional strength of the current study is the uniqueness of Oklahoma Medicaid data, in that the program operates under a fee-for-service model to afford full transparency relative to several other Medicaid programs [40]. To illustrate, fee-for-service Medicaid programs do not generally operate under federal waivers, with Oklahoma's program affording no mental health carve-outs [40].

Across previous studies using multi-state Medicaid populations to assess adherence, the proportion of members with a PDC  $\geq 80\%$  using PP1M has been reported to be significantly greater than comparator groups based upon multivariable analyses [19–22, 40]. Previous studies have also reported, via propensity score matching, that inpatient admissions were more frequent in cohorts that had lower PDC [19–22, 40]. In the current work, the bivariable analysis of both the continuous measure of PDC and dichotomous measure of PDC  $\geq 80\%$  versus  $< 80\%$  (i.e., adherent versus nonadherent) was not observed to significantly differ between PP1M/PP3Ms and OAP-switches. However, in the multivariable Lasso regression analysis, OAP-switches were significantly and independently associated with an 18.5% lower PDC compared with PP1M/PP3M after controlling for other factors ( $p = 0.030$ ). Whereas the current study's inclusion criteria included Medicaid members with either SCZ or SCD, other research that compared PP1M/PP3Ms with OAPs have applied varying inclusion criteria. To illustrate, the comparator groups of Manjelievskaia et al. [40], Pesa et al. [20], Pilon et al. [21], and Xiao et al. [22] included Medicaid members with any use of OAP and were limited to an SCZ diagnosis alone, while Patel et al. [19]

additionally required a hospitalization relapse following a medication's index date. Prior investigations have also utilized data from multiple, and structurally different, Medicaid programs. Manjelievskaia et al. [40] used Truven MarketScan Medicaid Multi-State data to include 439 members with PP1Ms ranging from 18 to 35 years of age, Pesa et al. [20] used Medicaid data to include 1939 members with PP1Ms, Pilon et al. [21] used Medicaid healthcare claims data from New Jersey, Iowa, Mississippi, Missouri, and Kansas to include 1107 members with PP1Ms, and Xiao et al. [22] used New Jersey, Iowa, Missouri, and Kansas Medicaid data to include 952 members with PP1Ms.

The current work assessed both the number and presence of 45-day treatment gaps in therapy for members initiating PP1Ms after a pre-index OAP versus those switching to another OAP. Controlling for other factors, the number of 45-day treatment gaps was 92.3% higher in OAP-switches compared with PP1M/PP3Ms ( $p = 0.004$ ). Two prior studies using multi-state Medicaid populations assessed various treatment gaps in patients with SCZ receiving an LAI or OAP [41, 42]. Marcus et al. [41] utilized Truven MarketScan Medicaid Multi-State data, including both first- and second-generation LAIs, and observed that LAIs were associated with a 55% lower adjusted odds of a 60-day treatment gap compared with OAPs (CI 0.34–0.60,  $p < 0.001$ ). That study, which included 940 members using LAIs, also compared outcomes for paliperidone palmitate versus OAPs in a subgroup analysis, wherein paliperidone palmitate was associated with a 27% lower adjusted odds of rehospitalization (CI 0.54–0.99,  $p < 0.041$ ) after controlling for several variables, including a 60-day treatment gap [41]. Pilon et al. [42] also compared second-generation LAIs to OAPs among 3307 Medicaid members from Iowa, Kansas, Missouri, and New Jersey. In a subgroup analysis of 2182, paliperidone palmitate was significantly associated with a higher persistence [i.e., a lack of 60-day therapy gaps (OR 1.53,  $p < 0.001$ )], with no significant differences in inpatient admissions, ED visits, or overall medical costs ( $p > 0.05$ ) [42]. Of note, the current study also observed that a lower number of 45-day treatment gaps was

significantly associated with PP1M/PP3Ms versus OAP-switches ( $p < 0.05$ ).

With regard to acute care readmissions, Lafeuille et al. [43] analyzed the risk of any all-cause inpatient readmission or ED revisit in patients recently hospitalized for SCZ that received either PP1M or an OAP during their initial inpatient stay. The authors utilized hospital-level data from the Premier Perspective Comparative Hospital Database and included patients from multiple third-party payers, including Medicaid [43]. Using multivariable analysis, PP1Ms were associated with a 39% lower adjusted risk of all-cause readmission to a hospital or ED compared with OAPs ( $p < 0.001$ ) [43]. Xiao et al. [44] compared adherence, inpatient admissions or ED visits), and costs across Medicaid members receiving PP1Ms or OAPs, reporting a significantly reduced risk of inpatient admission with PP1Ms (IRR 0.96,  $p < 0.01$ ), coupled with a reduced risk of 30-day readmissions (OR 0.89,  $p < 0.05$ ) and no significant difference in total healthcare costs ( $p > 0.05$ ). Tidmore et al. [45] observed among 2532 Oklahoma Medicaid members that LAI initiation in those with SCZ and/or BP was associated with significantly higher adjusted odds of admissions and readmissions compared with those initiating OAPs, also involving higher overall adjusted costs ( $p < 0.023$ ). Among those discharged from acute care settings, Tidmore et al. also reported that LAIs were subsequently associated with lower adjusted costs and shorter durations to psychiatry-related follow-up ( $p < 0.05$ ) [45]. As previously stated, the current study observed that PP1M/PP3M use was associated with a lower adjusted odds of all-cause readmissions compared with OAP-switches, with an OAP-switch incurring an 87.4% higher adjusted odds after controlling for  $PDC \geq 80\%$  ( $p = 0.003$ ) or a 91.1% higher odds when controlling for the presence of any 45-day treatment gap ( $p = 0.028$ ). Multivariable analyses also indicated that any 45-day treatment gap was associated with 2.717 times higher adjusted odds of any readmission ( $p = 0.003$ ), whereas a  $PDC \geq 80\%$  was associated with a 65.9% lower adjusted odds of readmission ( $p = 0.001$ ), which, overall, may be suggestive of important

clinical intervention points to mitigate SCZ or SCD resource utilization.

Bivariable analyses conducted by Patel et al. [19], Pesa et al. [20], Pilon et al. [21], and Xiao et al. [44] assessed differences in post-index total medical costs between PP1M and OAPs and reported no significant differences ( $p \geq 0.05$ ). Xiao et al. [22] employed marginal structural models, whereas both Manjelievskaia et al. [40] and Pilon et al. [42] utilized multivariable regression models and reported no significant differences in costs between groups ( $p \geq 0.05$ ). While the current study observed significantly lower unadjusted total medical costs in PP1M/PP3Ms compared with OAP-switches in both the pre-index ( $\$16,125 \pm 19,151$  versus  $\$31,634 \pm 32,534$ ,  $p < 0.001$ ) and post-index periods ( $\$46,998 \pm 43,791$  versus  $\$52,962 \pm 65,276$ ,  $p < 0.05$ ), the multivariable analysis of total costs indicated that OAP-switches were associated with an approximately 49% lower pre- to post-index change in costs relative to PP1M/PP3Ms ( $p < 0.001$ ). Notably, in the current work, improved adherence (i.e.,  $PDC \geq 80\%$ ) was associated with a 25.2% increase in pre-versus post-index costs ( $p = 0.032$ ) across the overall analysis and independent of treatment cohorts.

Certain limitations should be considered in interpreting the results of the current research endeavor. As with all nonrandomized observational studies, this work may have been subject to potential selection bias and residual confounding or confounding by indication, in part, owing to unmeasurable variables [29]. While proxies for case-mix severity and detailed disease categorization (e.g., SCZ type, year of initial SCZ or SCD diagnosis, comorbid mental health conditions) were included as covariates, no direct measure of disease severity is present within administrative claims (e.g., Positive and Negative Syndrome Scale) [46]. Additionally, measures of pre-index resource utilization and costs, demographics, provider types, and health system characteristics were included as potential predictors of outcomes. Without case notes and direct engagement of the provider and Medicaid member, the specific rationale or preferences surrounding medication switches at

the clinical case level could not be measured, nor could the clinical appropriateness of treatment changes be assessed. The comprehensive economic burden surrounding SCZ and SCD includes substantial indirect costs [2], which could not be assessed. Owing to the separation of and inability to link full federal/national Medicare data and state-specific Medicaid data, this investigation summarily excluded persons above 64 years of age (i.e., “dual-eligibles”). The sequelae and natural history of SCD and SCZ remain complex, with interventions and resource utilization requiring consideration of advancing age [47–49]. Caution should be applied in extrapolating findings to other payers, patients, or other Medicaid programs.

## CONCLUSION

This real-world multivariable investigation of adult Medicaid members with SCZ or SCD observed improved outcomes with PP1M/PP3Ms compared with OAP-switches. OAP-switches were also associated with poorer adjusted adherence, a greater adjusted number of treatment gaps, and a higher adjusted odds of any readmission. Medicaid members treated with PP1M/PP3M had significantly greater adherence and persistence and a lower odds of readmission relative to OAP-switches after controlling for numerous demographic, clinical, mental health, and provider characteristics. Although OAP-switches were associated with a lower change in adjusted pre- to post-index costs, the post-index total comprehensive direct medical costs did not differ between groups. Continued work should seek to assess and minimize poor adherence and persistence via targeted and supportive interventions in this vulnerable population.

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**Compliance with Ethics Guidelines.** This study was defined as exempt by the Office of Human Research Participant Protection (Institutional Review Board #12942) at the University of Oklahoma Health Sciences Center.

**Data Availability.** The datasets generated during and/or analyzed during the current study are not publicly available.

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