



# Health Outcomes Among Patients Diagnosed with Schizophrenia in the US Veterans Health Administration Population Who Transitioned from Once-Monthly to Once-Every-3-Month Paliperidone Palmitate: An Observational Retrospective Analysis

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Received: May 21, 2019  
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## ABSTRACT

**Introduction:** There is limited literature on treatment patterns, healthcare resource utilization (HRU), and costs among patients who transition from once-monthly paliperidone palmitate (PP1M) to once-every-3-month paliperidone palmitate (PP3M) in a real-world setting. Hence, this study compared treatment patterns, HRU, and costs 12-month pre- and post-PP3M transition among Veteran's Health Administration (VHA) patients with schizophrenia.

**Enhanced Digital Features** To view enhanced digital features for this article go to <https://doi.org/10.6084/m9.figshare.8966009>.

**Electronic supplementary material** The online version of this article (<https://doi.org/10.1007/s12325-019-01039-9>) contains supplementary material, which is available to authorized users.

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**Methods:** Patients with schizophrenia (aged  $\geq 18$  years) who initiated PP1M and transitioned per on-label criteria to PP3M (no treatment gap of  $> 45$  days in PP1M during the 4 months prior, same dose strength of the last two PP1M claims, and appropriate dose conversion from last PP1M to first PP3M claim) from January 2015 to March 2017 were included from the VHA database. The first transition date to PP3M was identified as the index date. Patients were required to have 12-month pre- and post-PP3M continuous health plan eligibility. Outcomes were compared using the Wilcoxon-signed rank and McNemar's test, appropriately.

**Results:** The study included 122 patients [mean (SD) age: 54 (13.7) years]. Pre- and post-PP3M transition, 64.8% and 61.5% of patients were adherent (proportion of days covered  $\geq 80\%$ ) to PP1M and PP3M, respectively. Comparison of HRU outcomes pre- and post-PP3M transition exhibited lower all-cause outpatient (37.5 vs. 31.1,  $p < 0.0001$ ) and pharmacy visits (56.1 vs. 46.7,  $p < 0.0001$ ). Similar trends were seen for mental health and schizophrenia-related outpatient and pharmacy HRU. Comparison of cost outcomes resulted in lower all-cause outpatient (\$27,221 vs. \$22,356,  $p = 0.0033$ ), higher pharmacy (\$16,349 vs. \$17,003,  $p = 0.0076$ ), lower total medical (\$35,834 vs. \$28,900,  $p = 0.0257$ ), and no difference in total costs (\$52,183 vs. \$45,903,  $p = 0.3118$ ). Similar trends were seen

for mental health and schizophrenia-related costs.

**Conclusions:** Transition to PP3M was associated with a decline in outpatient and pharmacy visits. All-cause medical cost reduction fully offset increased pharmacy costs among VHA patients with schizophrenia who transitioned from PP1M to PP3M.

**Funding:** Janssen Scientific Affairs.

**Keywords:** Antipsychotic agents; Healthcare costs; Schizophrenia; Medication adherence; Neurology; Paliperidone palmitate

## INTRODUCTION

Schizophrenia is a chronic and debilitating mental illness characterized by recurrent episodes of acute psychosis alternating with periods of full or partial remission [1]. It is a serious public health problem that affects approximately 1% of the US population and is considered 1 of the 20 leading causes of disabilities worldwide [2–4]. The estimated prevalence of schizophrenia and related psychotic disorders in the USA ranges between 0.25 and 0.64% [5]. Among US Veterans, a pooled prevalence of schizophrenia from 11 veteran studies was found to be up to 11% [6]. A retrospective claims-based study from October 2006 to September 2011 found nearly 60,000 incident cases of schizophrenia within the Veterans Affairs (VA) system [7].

Schizophrenia is considered the costliest mental illness and imposes a disproportionately large economic burden relative to other mental disorders that have been linked to early onset of the disease and its chronic nature with persisting symptoms [2, 4, 8, 9]. Furthermore, schizophrenia places a significant burden not only on patients but also families, caregivers, and the healthcare system [8]. US veterans with schizophrenia were found to occupy more hospital beds at any given time than veterans with any other illness [10]. Additionally, a recent study conducted in 2017 revealed that the average annual all-cause total healthcare costs among US veterans with schizophrenia was \$78,589 and \$82,895 for patients treated with paliperidone palmitate (PP) and oral atypical antipsychotics (OAA), respectively [11].

Schizophrenia is characterized by a complex psychopathology such as a diminished capacity for learning, working self-care, and interpersonal relationships [12]. Furthermore, schizophrenia patients experience a broad range of symptoms leading to a loss of function and autonomy. More than 50% of patients have intermittent but long-term psychiatric problems, and approximately 20% have chronic symptoms and disability [4, 13]. The foundation of treatment for schizophrenia patients—to help reduce disease severity and frequency of acute relapses—consists of antipsychotic (AP) agents including long-acting injectables (LAIs) and oral AP therapies (OATs) [14]. Despite the need for long-term, continuous therapy, patients often have difficulty with adherence to oral medication regimens [4, 15]. In 2009, the FDA approved a monthly atypical long-acting injectable antipsychotic therapy (LAT) once-monthly paliperidone palmitate (PP1M). Prior studies have shown that patients treated with PP1M had lower inpatient and long-term care admission and thus lower medical costs compared with patients treated with the first-line oral antipsychotic therapy [10].

In 2015, the FDA approved once-every-3-month paliperidone palmitate (PP3M). The advent of this new reduced dosing frequency therapy has been found to increase treatment adherence, and patients were shown to be more persistent on PP3M treatment [16, 17]. The administration of PP3M requires fewer clinical visits and thereby lower hospitalization rates and ultimately reduced healthcare resource utilization (HRU) and healthcare costs [16, 17]. In a post hoc analysis comparing median time to relapse across three different treatment trials, Weiden et al. discovered that after PP3M discontinuation, the time to relapse was much longer compared with PP1M [18]. Specifically, the study demonstrated that approximately 50% of patients who withdrew from PP3M were relapse free for approximately 13 months compared with the 6 months of relapse-free time for PP1M patients [18]. The findings by Weiden et al. imply that patients using PP3M remained stable for a longer period of time compared with PP1M patients, and PP3M may provide evidence for risk mitigation of schizophrenia patients

[18]. However, one study on the Medicaid population reported no significant difference in AP adherence, HRU, and costs before and after PP3M initiation [19]. Due to the availability of such mixed findings from published literature and the dearth of real-world evidence on the efficacy of PP3M, there is a significant need to authenticate such findings using real-world evidence. Hence, this study aimed to validate the existing findings on the effectiveness of PP3M among patients with schizophrenia by examining treatment patterns, HRU, and costs among patients who transitioned from PP1M to PP3M, in a real-world setting, utilizing the most recent VHA database.

## METHODS

### Objective

The main objective was to compare treatment patterns, HRU, and costs related to the 12 months pre- and post-transition from PP1M to PP3M as per on-label criteria to PP3M among VHA patients diagnosed with schizophrenia.

### Data Source

This was a retrospective cohort study utilizing data from the Veterans Health Administration (VHA) from January 1, 2014, to March 31, 2018 (the study period).

The VHA is the largest integrated healthcare system in the USA. The US Department of Veterans Affairs estimates that in 2014 there were slightly over 21 million living US military veterans. In the same year, the department provided medical services to ~ 6 million veterans and to over 700,000 non-veterans. This included services for active duty and reserve military personnel, spousal collateral, consultations and instruction, CHAMPVA workload, reimbursable workload with affiliates, humanitarian care, and occupational immunizations for employees, such as hepatitis A and B and flu vaccinations [20].

The VHA Medical Statistical Analysis System (SAS)<sup>®</sup> data sets are national administrative data

for VHA-provided healthcare utilized primarily by veterans but also by some non-veterans (e.g., employees, research participants). The data sets are provided in SAS format by fiscal year (October 1–September 30). These data are extracted from the National Patient Care Database as maintained by the VHA Office of Information at the Austin Information Technology Center, the central repository for VA data. The stability of VHA data sources allows for superior analysis of the continuity of care of patients over multiple years.

No identifiable patient information or medical records were disclosed for the purposes of this study except in compliance with applicable law. Since the core study did not involve the collection, use, or transmittal of individual identifiable data, institutional review board approval to conduct this study was not required.

### Study Population

Patients included in the study were aged  $\geq 18$  years. Those selected had  $\geq 1$  encounter that included a schizophrenia diagnosis [International Classification of Diseases, Ninth and Tenth Revision, Clinical Modification (ICD-9/10-CM) code: 295.XX (excluding 295.7 schizoaffective disorder), ICD-10-CM: F20.XX, F21] during the study period (January 1, 2014–March 31, 2018); had initiated treatment with PP1M between January 1, 2015, and March 31, 2017 (the identification period); and had continuous health plan enrollment for 12 months pre- and post-follow-up date. Patients must also have transitioned from PP1M to PP3M as per on-label criteria during the identification period. The first dispensing of PP1M was defined as the PP1M date, and the index date was defined as the first date of dispensing PP3M. Patients were excluded from the study if they had evidence of PP3M during the baseline period.

On-label criteria included patients that transitioned from PP1M to PP3M and had at least 4 months of PP1M use prior to initiation of PP3M with no treatment gap of  $> 45$  days in PP1M coverage in the 4 months prior to PP3M

initiation. Patients were on-label if they had the same dose strength from the last two PP1M claims prior to transition to PP3M transition and had the appropriate dosage conversion between the last PP1M and first PP3M claims (78–273 mg, 117–410 mg, 156–546 mg, or 234–819 mg) as per prescribing guidelines. PP3M dispensations were identified through the National Drug Codes (NDC; 50458-606-01, 50458-607-01, 50458-608-01, and 50458-609-01).

### Demographic and Baseline Clinical Characteristics

Patients demographics including age, sex, and race were assessed. Additionally, clinical characteristics including the Quan-Charlson comorbidity index (Q-CCI) score, other individual comorbidities [including mental health (MH)-related diagnoses such as post-traumatic stress disorder, anxiety, tobacco use, bipolar disorder, any depression disorder, and substance abuse] and non-MH-related diagnoses [including obesity, diabetes mellitus, cardiovascular disease (CVD)-hyperlipidemia, CVD-hypertension, and chronic obstructive pulmonary disease] were recognized using ICD-9-CM codes [see Supplementary Appendices (S), Appendix 1]. All ICD-9 diagnostic and procedure codes were mapped to ICD-10 codes based on the general equivalence mappings (GEMs) published by the Centers for Medicare and Medicaid Services (CMS) [21].

### Outcome Measures

Outcome measures including treatment patterns, HRU, and costs during the 12-month pre- and post-PP3M initiation were measured. Moreover, treatment patterns among patients who transitioned from PP1M to PP3M were measured as the proportion of patients prescribed APs [including any oral, LAI, and short-acting injectable (SAI) (S: Appendices 2 and 3)] and other MH-related medications [antidepressants, anxiolytics, and mood stabilizers (S: Appendix 4)]. Furthermore, medication adherence was calculated using proportion of days covered (PDC) defined as number

of days in the follow-up period “covered” by medication divided by follow-up time (i.e., 12 months) and was reported as  $\geq 80\%$  as adherent and  $< 80\%$  as non-adherent [22]. The medication possession ratio (MPR) was also used to assess adherence and was defined as the number of days of supply (i.e., number of days a prescription is supposed to last) within the entire exposure to therapy. The exposure was defined as the number of days between the date of the first drug fill and the last drug refill plus the number of days of supply of the last refill. The MPR was then computed as the sum of the days of supply divided by the exposure to therapy.

All-cause, MH-related, and schizophrenia-related HRU (e.g., inpatient stays, outpatient pharmacy visits, outpatient visits, inpatient length of stay) and costs (e.g., inpatient, outpatient, pharmacy, total medical, and total costs) were assessed and compared during the 12-month pre- and post-PP3M transition. Medical claims were considered MH-related if there was a mental health disorder (S: Appendix 5) and/or schizophrenia diagnosis (as defined previously) in any position on the claim. MH-related pharmacy costs included costs for any AP (S: Appendices 2 and 3) and/or other MH-related (S: Appendix 4) medications. Medical costs were considered schizophrenia-related if there was a schizophrenia diagnosis in any position on the claim. Schizophrenia-related pharmacy costs included costs for any AP (S: Appendices 2 and 3). All costs were adjusted to 2017 US dollars using the medical care component of the consumer price index (CPI).

### Statistical Analysis

Demographics and baseline clinical characteristics were examined descriptively among PP1M users who transitioned to PP3M as per on-label criteria. To compare the 12 months of pre- and post-PP3M transition, outcomes such as treatment patterns, HRU, and healthcare costs were analyzed using the Wilcoxon signed-rank test for continuous variables and McNemar’s test for categorical variables. The level of significance was set at  $\alpha = 0.05$ . All the analyses were conducted using SAS<sup>®</sup> statistical software (version 9.3, SAS Institute, Cary, NC, 2012).

## RESULTS

Based on the inclusion criteria, there were 3627 patients who initiated treatment with PP1M during the identification period. Among the 3627 patients identified, 122 met the remaining inclusion/exclusion criteria of transitioning from PP1M to on-label use of PP3M as shown in Fig. 1.

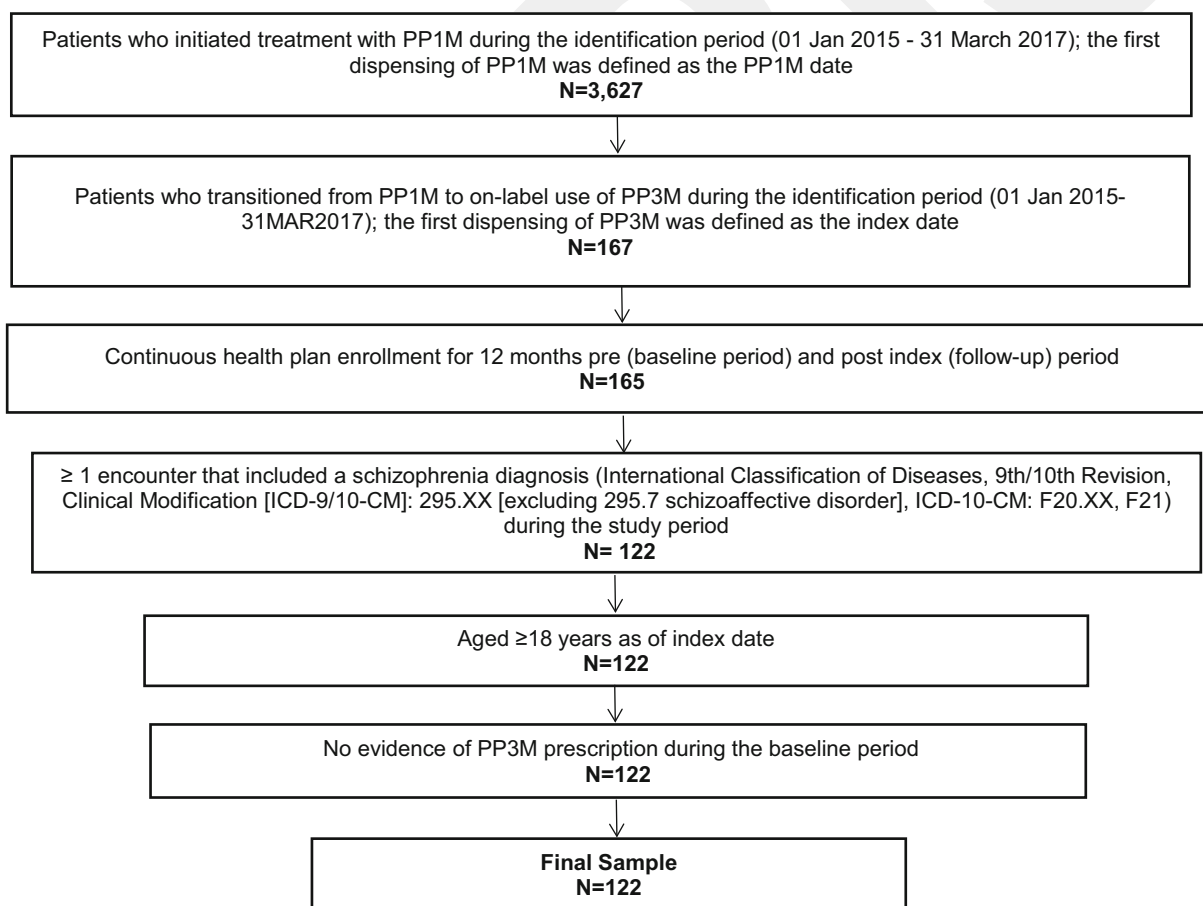
### Demographics and Baseline Characteristics

The average age of on-label PP1M users who transitioned to PP3M was 54 years. A majority of the patients belonged to the age group of 55–64 years (36.1%), and 24.6% were  $\geq$  65 years. Patients were predominantly male

(91.8%) and white (54.1%). The mean Q-CCI score of schizophrenia patients was 0.9. The most common MH-related comorbidities were substance abuse (34.4%) followed by any depression disorder (33.6%) and tobacco use (28.7%). Furthermore, the most common non-MH-related comorbidities were CVD-hypertension (38.5%) and CVD-hyperlipidemia (38.5%) followed by diabetes mellitus (26.2%) and obesity (21.3%) (Table 1).

### Treatment Patterns During Pre- and Post-Transition to PP3M

During the pre- and post-transition to PP3M, the use of antidepressants was significantly higher in the 12 months pre-PP3M initiation compared with the 12 months post-PP3M



**Fig. 1** Patient selection criteria for transition to on-label PP3M. *PP1M* once-monthly paliperidone palmitate, *PP3M* once-every-3-month paliperidone palmitate

**Table 1** Comparison of treatment patterns 12-month pre- and post-PP3M transition among VHA patients treated with PP1M

Treatment patterns 12-month pre- and post-PP3M transition	12-month pre-PP3M transition (N = 122) N (%)	12-month post-PP3M transition (N = 122) N (%)	p value*
<b>AP use</b>			
Any oral APs	60 (49.2%)	51 (41.8%)	0.0947
Atypical oral APs	57 (46.7%)	48 (39.3%)	0.0947
Any LAI APs	122 (100.0%)	122 (100.0%)	–
Atypical LAI APs	122 (100.0%)	122 (100.0%)	–
Antidepressants	78 (63.9%)	68 (55.7%)	0.0075*
Anxiolytics	58 (47.5%)	55 (45.1%)	0.5637
Mood stabilizers	57 (46.7%)	53 (43.4%)	0.2850
<b>PDC</b>			
PDC by any agent mean ± SD [median]	0.9 ± 0.1 [0.9]	0.9 ± 0.2 [1.0]	0.7770
≥ 80%	110 (90.2%)	104 (85.2%)	0.2999
PDC by PP1M mean ± SD [median]	0.8 ± 0.2 [0.8]	0.1 ± 0.2 [0.0]	< 0.0001*
≥ 80%	79 (64.8%)	0 (0.0%)	–
PDC by PP3M mean ± SD [median]	–	0.8 ± 0.3 [0.9]	–
≥ 80%	–	75 (61.5%)	–
<b>MPR</b>			
MPR by any agent mean ± SD [median]	1.0 ± 0.1 [1.0]	1.0 ± 0.1 [1.0]	0.9264
≥ 80%	116 (95.1%)	115 (94.3%)	0.7815
MPR by PP1M mean ± SD [median]	0.8 ± 0.2 [0.9]	0.1 ± 0.2 [0.0]	< 0.0001*
≥ 80%	91 (74.6%)	4 (3.3%)	< 0.0001*
MPR by PP3M mean ± SD [median]	–	0.8 ± 0.3 [1.0]	–
≥ 80%	–	82 (67.2%)	–

AP antipsychotic, LAI long-acting injectable, MPR medication possession ratio, PP1M once-monthly paliperidone palmitate, PP3M once-every-3-month paliperidone palmitate

\*Significant at  $p < 0.05$

transition period (63.9% vs. 55.7%,  $p = 0.0075$ ). There was no significant difference in the use of any APs, anxiolytics, or mood stabilizers upon comparison of 12 months pre- and post-PP3M initiation.

Adherence, as defined by PDC and MPR, revealed that during the pre-PP3M transition, 64.8% and 74.6% of patients were adherent ( $\geq 80\%$ ) to PP1M, respectively. During the post-PP3M transition, PDC and MPR showed that 61.5% and 67.2% of patients were adherent ( $\geq 80\%$ ) to PP3M, respectively (Table 1).

### HRU During the Pre- and Post-Transition to PP3M

During the 12-month pre-PP3M transition, patients had a significantly higher number of all-cause outpatient (37.5 vs. 31.1,  $p < 0.0001$ ) and pharmacy visits (56.1 vs. 46.7,  $p < 0.0001$ ) compared with the post-PP3M period. Significantly more MH-related outpatient (23.5 vs. 16.0,  $p < 0.0001$ ) and pharmacy visits (48.3 vs. 37.4,  $p < 0.0001$ ) were observed for patients during the pre- vs. post-PP3M transition period. Similarly, patients had significantly more mean schizophrenia-related outpatient (15.4 vs. 8.1,  $p < 0.0001$ ) and pharmacy visits (27.4 vs. 18.7,  $p < 0.0001$ ) during the pre- vs. post-PP3M transition (Table 2).

### Costs During the Pre- and Post-Transition to PP3M

Among VHA patients, a significant decrease was observed for all-cause outpatient costs from pre-PP3M to post-PP3M transition (\$27,221 vs. \$22,356,  $p = 0.0033$ ). As such, the total all-cause medical (in- and outpatient) costs significantly declined from pre-PP3M to post-PP3M transition (\$35,834 vs. \$28,900,  $p = 0.0257$ ). However, all-cause pharmacy costs were slightly lower during the pre-PP3M transition compared with post-PP3M (\$16,349 vs. \$17,003,  $p = 0.0076$ ). As a result, the all-cause total cost did not result in any significant difference from pre- to post-PP3M transition (\$52,183 vs. \$45,903,  $p = 0.3118$ ) (Table 2).

A significant decrease from pre-PP3M to post-PP3M transition was also observed for mean number of MH-related outpatient costs (\$23,120 vs. \$17,561,  $p < 0.0001$ ). Total MH-related medical costs also significantly declined from pre- to post-PP3M (\$31,219 vs. \$24,105,  $p = 0.0005$ ). However, MH-related pharmacy costs significantly increased from pre- to post-PP3M transition (\$14,826 vs. \$15,999,  $p = 0.0067$ ). Therefore, the total MH-related costs were found to be comparable during the pre- and post-PP3M transition (\$46,045 vs. \$40,104,  $p = 0.0734$ ) (Table 2).

Furthermore, findings on schizophrenia-related healthcare costs revealed a similar trend to all-cause and MH-related costs. Study results indicated that schizophrenia-related outpatient costs were significantly higher during the pre-PP3M transition compared with the post-PP3M transition (\$13,724 vs. \$9701,  $p < 0.0001$ ). Total medical costs were also significantly higher during the pre-PP3M transition (\$16,179 vs. \$11,255,  $p = 0.0001$ ). On the other hand, schizophrenia-related pharmacy costs were higher during the post-PP3M period (\$14,365 vs. \$15,793,  $p = 0.0018$ ). Due to the high pharmacy costs during the post-PP3M transition, the total schizophrenia-related healthcare costs remained similar during the pre- and post-PP3M transition (\$30,544 vs. \$27,047,  $p = 0.3305$ ) as illustrated in Table 2.

## DISCUSSION

This retrospective claims-based study comprehensively assessed the treatment patterns and economic burden of schizophrenia patients that transitioned from PP1M to PP3M. PP3M is recommended for use after the initiation of PP1M and establishment of at least 4 months of effective treatment [23]. Prior research has shown that the transition to PP3M was associated with improved therapy adherence, reduced hospitalization rates, and thereby reduced HRU and healthcare costs [16, 17]. However, one Medicaid study reported no significant difference in AP adherence, HRU, and costs before and after PP3M initiation [19]. Due to the availability of such varied findings from

**Table 2** Comparison of healthcare resource utilization during the 12-month pre- and post-PP3M transition among VHA patients treated with PP1M

12-month pre- and post-PP3M transition HRU	12-month pre-PP3M transition ( <i>N</i> = 122) <i>N</i> (%)	12-month post-PP3M transition ( <i>N</i> = 122) <i>N</i> (%)	<i>p</i> value*
All-cause HRU			
Number of patients			
Any inpatient stay	25 (20.5%)	23 (18.9%)	0.7150
Any pharmacy visit	122 (100.0%)	122 (100%)	–
Any outpatient visit	122 (100.0%)	122 (100%)	–
Number of visits (mean ± SD)			
Inpatient length of stay (LOS) [days]	5.7 ± 17.8	4.4 ± 13.9	0.2158
Number of inpatient stays	0.5 ± 1.4	0.5 ± 1.3	0.8947
Number of outpatient visits	37.5 ± 20.4	31.1 ± 22.0	< 0.0001*
Number of pharmacy visits	56.1 ± 39.2	46.7 ± 35.7	< 0.0001*
Mental health-related HRU			
Number of patients			
Any inpatient stay	25 (20.5%)	23 (18.9%)	0.7150
Any pharmacy visit	122 (100.0%)	122 (100%)	–
Any outpatient visit	122 (100.0%)	122 (100%)	–
Number of visits (mean ± SD)			
Inpatient length of stay (LOS) [days]	5.6 ± 17.6	4.4 ± 13.9	0.2788
Number of inpatient stays	0.4 ± 1.0	0.4 ± 1.1	0.9937
Number of outpatient visits	23.5 ± 10.0	16.0 ± 10.1	< 0.0001*
Number of pharmacy visits	48.3 ± 35.2	37.4 ± 30.6	< 0.0001*
Schizophrenia-related HRU			
Number of patients			
Any inpatient stay	10 (8.2%)	12 (9.8%)	0.6171
Any pharmacy visit	122 (100.0%)	122 (100%)	–
Any outpatient visit	115 (94.3%)	110 (90.2%)	0.0956
Number of visits (mean ± SD)			
Inpatient length of stay (LOS) [days]	1.6 ± 7.0	1.4 ± 6.6	0.8672
Number of inpatient stays	0.1 ± 0.7	0.1 ± 0.4	0.9988

**Table 2** continued

12-month pre- and post-PP3M transition HRU	12-month pre-PP3M transition ( <i>N</i> = 122) <i>N</i> (%)	12-month post-PP3M transition ( <i>N</i> = 122) <i>N</i> (%)	<i>p</i> value*
Number of outpatient visits	15.4 ± 5.5	8.1 ± 4.8	< 0.0001*
Number of pharmacy visits	27.4 ± 29.3	18.7 ± 24.5	< 0.0001*
All-cause costs (mean ± SD)			
Inpatient stay costs	\$8613 ± \$23,358	\$6544 ± \$22,610	0.2082
Outpatient visit costs	\$27,221 ± \$23,602	\$22,356 ± \$18,981	0.0033*
Pharmacy costs	\$16,349 ± \$11,028	\$17,003 ± \$9155	0.0076*
Total medical (outpatient + inpatient) costs	\$35,834 ± \$38,093	\$28,900 ± \$32,210	0.0257*
Total (medical + pharmacy) costs	\$52,183 ± \$43,942	\$45,903 ± \$35,245	0.3118
Mental health-related costs (mean ± SD)			
Inpatient stay costs	\$8099 ± \$22,298	\$6544 ± \$22,610	0.2759
Outpatient visit costs	\$23,120 ± \$19,859	\$17,561 ± \$16,038	< 0.0001*
Pharmacy costs	\$14,826 ± \$6787	\$15,999 ± \$7316	0.0067*
Total medical (outpatient + inpatient) costs	\$31,219 ± \$33,729	\$24,105 ± \$30,043	0.0005*
Total (medical + pharmacy) costs	\$46,045 ± \$35,466	\$40,104 ± \$31,822	0.0734
Schizophrenia-related costs (mean ± SD)			
Inpatient stay costs	\$2455 ± \$10,935	\$1553 ± \$5800	0.8317
Outpatient visit costs	\$13,724 ± \$15,255	\$9701 ± \$13,230	< 0.0001*
Pharmacy costs	\$14,365 ± \$6379	\$15,793 ± \$7250	0.0018*
Total medical (outpatient + inpatient) costs	\$16,179 ± \$21,255	\$11,255 ± \$15,308	0.0001*
Total (medical + pharmacy) costs	\$30,544 ± \$21,579	\$27,047 ± \$16,589	0.3305

HRU healthcare resource utilization, PP1M once-monthly paliperidone palmitate, PP3M once-every-3-month paliperidone palmitate, SD standard deviation

\*Significant at  $p < 0.05$

published literature and the scarcity of real-world evidence on the efficacy of PP3M, this study set out to address these concerns in a real-world setting.

The study findings showed that there was an improvement in clinical outcomes such as the significant decline of antidepressant use post-

PP3M transition. While previous literature has not reported a decline in the use of antidepressants associated with PP3M transition, the current study warrants further research into the decline of antidepressants for validation, reasons for discontinuation, and implications of antidepressant use for HRU and costs.

There was also an improvement in HRU with the observation of a significantly lower number of all-cause, MH-, and schizophrenia-related outpatient and outpatient pharmacy visits post-PP3M transition. In support of our findings, a 2018 study by DerSarkissian et al. illustrated that veterans had fewer outpatient visits during the post-PP3M transition [16]. A reason for the reduction in outpatient and outpatient pharmacy visits could be the reduction in dosing frequency, as PP3M is administered once every 3 months as opposed to the once-monthly PP1M. Furthermore, the added flexibility of the once-every-3-month dosing option for PP3M leads to improved adherence, which, in turn, can greatly affect recovery and quality of life and ultimately reduce HRU. Several other studies also support the notion of reduced dosing frequency and its association with improved adherence [24–26]. In another 2018 study, Lai et al. reported that patients who switched from PP1M to PP3M were found to have quality of life benefits due to the decreased number of visits for injections. A lower frequency of injections allows for patients to gain more control of their daily lives and gives patients fewer reminders of their illness burdens [27]. A study by Einarson et al. in 2017 found that less frequent administrations are also associated with fewer negative effects such as reduced injection site pain and less disruption of daily activities. Reduced dosing frequency can also give patients more time for other activities such as rehabilitation [28]. Additionally, as the administration of PP3M is required only four times per year, physicians, nurses, and caregivers are given more freedom—allowing for a better use of resources in the overburdened healthcare system [28, 29]. Overall, nonadherence to treatment is prevalent among patients with schizophrenia undergoing antipsychotic therapy, and nonadherence presents an increased risk of relapse and hospitalization for patients. However, the reduced dosing frequency of PP3M may greatly benefit patients not only in terms of HRU but also in providing the benefit of improved quality of life.

Significantly lower all-cause, MH-, and schizophrenia-related costs post-PP3M transition were observed for outpatient and total medical costs. Furthermore, while the numeric values for all-cause, MH-, and schizophrenia-

related costs were lower during the post-PP3M transition compared with the pre-PP3M transition, the cost difference was not statistically significant. Despite the offset in total cost, there could still be some financial impact on payers. In the similar study by DerSarkissian et al., a significant decrease was not only observed for in- and outpatient costs, but also for total costs during the study's 6-month post-PP3M transition compared with the pre-transition period, which could be indicative of an overall cost saving during post-PP3M transition. Specifically, DerSarkissian et al. observed significant inpatient cost savings of approximately \$2300 compared with the non-significant savings of \$2000 in the current study. However, the study only investigated HRU and costs 6 months pre- and post-transition to PP3M. The differences in study times may have been because of the differences in findings. A longer study time pre- and post-transition can accumulate more data on patients but would introduce more extraneous factors that may influence results. A 2018 claims-based study by Emond et al., using Medicaid data, elected for a study period of 6 months pre- and 12 months post-transition and observed an offset in healthcare costs—like the current study. Emond et al. remarked that if a 12-month pre-initiation period was used in the study then HRU and costs could be captured during a time where patients may not yet have been stabilized on PP1M. These results and remarks by Emond et al. warrant future analysis of study time consideration for pre- and post-transition periods and how it may affect results.

Additionally, the possible driver for total cost offset in the current study could be the pharmacy cost, which was approximately \$650 higher during the post-PP3M transition. Brasso et al. and Daghistani et al. noted that three doses of PP1M are the equivalent of one PP3M dose; however, the administrations are reduced by 66%. These studies explain the current study's findings where pharmacy costs were higher during the post-PP3M period leading to an offset in costs after accounting for other healthcare costs. Despite this cost offset, PP3M can provide a clinical benefit to patients in terms of convenience of dosing frequency,

which may be associated with improved quality of life.

While claims data are extremely valuable for the efficient and effective examination of healthcare outcomes, treatment patterns, and HRU and costs, claims data are collected for the purpose of payment and not research. Therefore, claims data can have coding inaccuracies and missing data. With claims data, adherence is evaluated on the presence of a claim and does not indicate if a medication has been taken as prescribed, especially for oral medications, and can therefore overestimate patient adherence. In addition, cost results may only be generalizable to the US because the data included VHA patients in the US and medical costs were adjusted to US dollars. It should also be noted that while the standard deviations for costs were large, this can be attributed to the small sample size or the scale of costs. Furthermore, the current study only focused on the direct HRU and costs for patients with schizophrenia pre- and post-PP3M transition. Indirect cost benefits of PP3M transition for patients with schizophrenia such as productivity and employment may be of interest for future studies.

The baseline of 12 months may not capture the first PP1M use for the subset of patients that may have been on PP1M much longer. The pre-post study design comes with limitations such as that the differences in the outcome of interest may not be fully attributable to the specific intervention. Moreover, the study did not account for changes in patient characteristics before and after the PP3M use when assessing the change in outcomes. While the duration of effect for LAIs is independent of further action by patients, future research using longer follow-up times may help to confirm findings on PP3M transition benefits [30].

Nevertheless, the study's strength comes from the use of patients as their own controls. Finally, results may not be generalizable to the entire US population, as the study only included VHA patients who sought out healthcare through the VHA system, wherein patients may have different characteristics and comorbidities compared with the general population. Patients in the VHA system are also predominantly males and of lower socioeconomic status, and a high proportion of patients are aged 55 years and older. Furthermore,

because the current study focused on the transition of PP1M to PP3M per an on-label basis, results may not be generalizable outside of the sample used. Moreover, the smaller sample size may be attributed to the fact that oral antipsychotic therapies are considered the first-line of therapy for patients with schizophrenia before LAI initiation [10, 31]. Last, as stated previously, PP3M is generally recommended after the effective establishment of PP1M treatment for at least 4 months [23].

## CONCLUSIONS

This study demonstrated the transition to PP3M from PP1M was associated with a significant decline in all-cause outpatient and pharmacy visits among VHA patients with schizophrenia. Furthermore, there was a reduction in all-cause medical costs fully offsetting the incremental all-cause pharmacy costs from 12-month pre- and post-PP3M transition. These findings exhibit the potential improvement of clinical and economic outcomes when considering adequately treated PP1M patients for PP3M therapy. In addition, a substantial decrease was observed in concomitant medication use, such as antidepressants, among patients during the post-PP3M transition. While this analysis was limited to the outcomes assessable in the claims database, future studies should assess the impact of the every-3-month therapeutic option on humanistic outcomes such as quality of life for those patients maintained on PP1M.

## ACKNOWLEDGEMENTS

**Funding.** This study and the Rapid Service Fee were funded, without restriction, by Janssen Scientific Affairs, LLC, 920 Rte. 202, Raritan, NJ, 08869. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis.

**Medical Writing, Editorial, and Other Assistance.** Research assistance in the

preparation of this article was provided by Jien Li and Catherine Callan of SIMR, LLC, and Richa Bashyal, a former employee of the same. Administrative assistance was provided by Michael Kane of SIMR, LLC. Support for this assistance was funded by Janssen Scientific Affairs, LLC.

**Authorship.** All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

**Disclosures.** Along Huang is an employee of SIMR, LLC, a paid consultant to Janssen Scientific Affairs. Li Wang is an employee of SIMR, LLC, a paid consultant to Janssen Scientific Affairs. Charmi Patel is an employee of Janssen Scientific Affairs and stockholders of Johnson & Johnson. Onur Baser consults for SIMR, LLC. AEK is an employee of Janssen Scientific Affairs and stockholders of Johnson & Johnson. Kruti Joshi is an employee of Janssen Scientific Affairs and stockholders of Johnson & Johnson.

**Compliance with Ethics Guidelines.** Neither institutional review board approval nor consent was necessary for this study, as it was a retrospective analysis conducted with de-identified data; no identifiable patient information or medical records were disclosed for the purposes of this study except in compliance with applicable law. Since the core study did not involve the collection, use, or transmittal of individual identifiable data, the conduct of this study was exempt from institutional review board approval, per the Federal Policy for the Protection of Human Subjects (1991).

**Data Availability.** The datasets generated and analyzed during the current study are included in the published version.

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