



The Impact of Once-Monthly Paliperidone Palmitate on Healthcare Utilization Among Patients With Schizophrenia Treated in an Integrated Healthcare System: A Retrospective Mirror-Image Study

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ABSTRACT

Introduction: Previous evidence demonstrated that patients with schizophrenia consumed substantial healthcare resources in an integrated healthcare system. This study evaluated the impact of initiating once-monthly paliperidone palmitate (PP1M) on healthcare resource utilization (HRU) among patients with schizophrenia treated in a US integrated healthcare system.

Methods: This retrospective study used electronic medical records from Atrium Health. Adults with at least two diagnoses of schizophrenia who received an initial PP1M

dose between September 2009 and April 2019 (the corresponding date defined the index date) and at least one subsequent dose within 90 days were included. Additionally, patients were required to have received active care (at least one healthcare visit every 6 months) during 12-month pre- and post-index periods and at least one oral antipsychotic prescription during the 12-month pre-index period. Inpatient, emergency room (ER), and outpatient visits were compared over 12-month pre- versus post-index periods within the same cohort using McNemar's and Wilcoxon signed rank tests. Findings were reported for all patients and separately in patients with at least one schizophrenia relapse (schizophrenia-related inpatient or ER visit) during the 12-month pre-index period.

Results: The study cohort included 210 patients (mean age 34.2 years, 69.5% male, 39.1% had Medicaid). From the 12-month pre- to post-index period, the proportion of patients with visits and mean number of visits reduced for all-cause inpatient (67.6% to 22.4%, 1.2 to 0.4), 30-day readmission (12.4% to 2.4%, 0.2 to 0.1), and ER (68.6% to 45.7%, 2.3 to 1.2) visits, whereas the mean number of outpatient visits increased (8.7 to 11.6) (all $P < 0.05$). Similar trends were observed for mental health- and schizophrenia-related HRU. The trends in HRU in patients with prior relapse were similar with a higher extent of reduction in inpatient and ER use compared to the overall cohort.

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Conclusion: Initiation of PP1M was associated with reduced acute HRU in patients with schizophrenia, indicating potential clinical and economic benefits, especially in patients with prior relapse.

Keywords: Healthcare resource utilization; Once-monthly paliperidone palmitate; Retrospective cohort study; Schizophrenia

Key Summary Points

Why carry out this study?

Long-acting injectable (LAI) antipsychotics, which have reduced frequency of administration compared to oral antipsychotics, are expected to improve adherence, a common challenge in patients with schizophrenia.

Once-monthly paliperidone palmitate (PP1M) is a commonly used LAI antipsychotic in patients with schizophrenia.

Prior studies examining the real-world health impact of PP1M included specific patient populations (e.g., patients with certain types of health insurance such as Medicaid or Medicare Advantage or Veterans Affairs beneficiaries) and therefore had limited generalizability.

This study examined the impact of PP1M on healthcare utilization among patients with schizophrenia treated in an integrated healthcare system in the USA.

What was learned from this study?

Acute healthcare utilization (inpatient and emergency room visits and readmissions) during 12 months after PP1M initiation reduced significantly compared to 12 months before PP1M initiation, indicating the potential clinical and economic benefits of PP1M.

The findings of this study involving patients with different types of insurances and those without insurance complement the findings from previous studies on this topic conducted in specific settings and contribute to the holistic picture of the real-world health impact of PP1M.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.13573862>.

INTRODUCTION

Schizophrenia is a serious chronic neurodegenerative mental disorder that is characterized by distortion in thoughts, perception, behavior, and speech [1, 2]. The condition is associated with positive or negative symptoms. Positive symptoms of schizophrenia may include hallucinations, delusions, and disorganized speech and behaviors, and negative symptoms may include reduced affect, inability to feel pleasure, lack of motivation, and lack of speech [1, 3]. Schizophrenia is one of the top 15 reasons for disability worldwide, affecting around 1.1% of the adult population in the USA [4, 5]. The average life expectancy of patients with schizophrenia is shorter by 15–25 years compared to those without schizophrenia [6]. The reduced life expectancy is mainly due to comorbid conditions such as cardiovascular diseases, hyperlipidemia, diabetes, and substance use disorders, which are common in patients with schizophrenia [7]. Schizophrenia is associated with a significant social and economic burden. It has been reported that total annual costs attributable to schizophrenia are US \$155.7 billion including US \$9.3 billion direct medical costs and US \$117.3 billion indirect costs (e.g., unemployment and productivity loss due to caregiving) [8]. However, despite the

substantial costs associated with schizophrenia, this chronic disease does not receive the same amount of attention that is given to other chronic diseases.

Antipsychotic medications are a crucial aspect of schizophrenia treatment. Generally, lifelong treatment with antipsychotics is required to avoid symptom relapse in patients with schizophrenia. Second-generation antipsychotics such as paliperidone, quetiapine, and risperidone are used more commonly than first-generation antipsychotics such as chlorpromazine, fluphenazine, and haloperidol [9]. Adherence to antipsychotics is crucial in patients with schizophrenia and has been recognized as a national quality measure [10]. In clinical practice, adherence to oral antipsychotics has been reported to be a challenge in patients with schizophrenia, with reported non-adherence rates of over 50% [11, 12]. Non-adherence to antipsychotics is associated with an increased risk of symptom relapses, hospitalizations, and emergency room (ER) visits and higher healthcare costs [13, 14]. It has been reported that patients who discontinue antipsychotic treatment are three times more likely to experience a symptom relapse within 1 year compared to those who continue their treatment [15, 16]. A multisite prospective study examining the impact of medication nonadherence in patients with schizophrenia found that medication nonadherence was associated with 55% higher odds of being hospitalized, 49% higher odds of having an ER visit, and 122% higher odds of being arrested [17]. Medication nonadherence is responsible for more than US \$1 billion hospitalization costs annually in patients with schizophrenia in the USA [18]. Long-acting injectable (LAI) antipsychotics, despite having similar clinical efficacy as oral antipsychotics [19], are expected to have superior real-world effectiveness primarily due to better adherence because of reduced frequency of administration. Newly released guidelines from the American Psychiatric Association recommend LAIs as an alternative therapy to oral antipsychotics in patients with a history of poor or uncertain adherence, and/or when patients are transitioning between inpatient and outpatient settings [20]. Other

guidelines recommend second-generation LAIs as an initial treatment option for patients with schizophrenia, after sufficient efficacy and tolerability has been established with the oral formulation of the same antipsychotic agent [21, 22].

Once-monthly paliperidone palmitate (PP1M), a long-acting injectable dosage form of paliperidone, was approved by the US Food Drug Administration in September 2009 for emergent and maintenance treatment of schizophrenia. Prior studies have shown that use of PP1M was associated with increased medication adherence and reduced inpatient visits, 30-day readmissions, length of stay, and ER visits [23–31]. These studies have involved patients with certain types of insurance such as Medicaid and Medicare Advantage or specific patient populations such as Veteran Affairs patients. Scant research has been conducted from the perspective of an integrated healthcare system, which includes patients with different types of insurances and those without insurance. An integrated healthcare system involves collaborative and coordinated care provided by a commonly owned network of healthcare providers such as physicians, hospitals, and urgent care clinics [32]. There are currently more than 600 integrated healthcare systems in the USA [33]. As a result of the emphasis on care continuity and commonly adopted standards of care, the integrated healthcare system model has been associated with increased quality of care compared to fragmented healthcare settings [34]. Previous analyses revealed that patients with schizophrenia treated within a US integrated healthcare system had low rates of routine/follow-up care visits and high rates of acute healthcare visits, indicating a need to re-evaluate health management strategies and improve treatment outcomes [35]. We conducted a retrospective mirror-image study among patients with schizophrenia treated in an integrated healthcare system in the USA who were initiated on PP1M after previously being on oral antipsychotic therapy. Healthcare resource utilization (HRU) during the 12 months after PP1M initiation was compared to HRU during the 12 months before PP1M initiation.

METHODS

Data Source

A retrospective cohort study was conducted using data from Atrium Health's electronic medical records (EMRs) from January 2008 to April 2020. Atrium Health is a large integrated healthcare system located in the southeastern USA. There are over 900 care locations within the system including hospitals, physician practices, urgent care centers, surgery centers, rehabilitation facilities, home health centers, and nursing homes in the states of North Carolina, South Carolina, and Georgia. A common EMR system is used for all the facilities and data on over 10 million patient visits annually is captured within the EMR data warehouse. The EMR data warehouse contains data on sociodemographics including age, race/ethnicity, gender, and health insurance status; details regarding healthcare visits such as admission and discharge time-stamps and the International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification (ICD-9-CM/ICD-10-CM) diagnosis and procedure codes associated with the visit; results of laboratory tests; medication orders including dose, prescribing physician; and administration of injectable medications.

Study Protocol Approval

The study protocol was approved by Advarra Institutional Review Board (Reference Number Pro00034063). This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

Study Population

The study cohort consisted of patients who received an administration of PP1M from September 2009 to April 2019 followed by at least one additional administration of PP1M within 90 days, with the earlier administration date defined as the index date. Eligible patients were aged 18 years or more on the index date and had at least two healthcare visits with an

ICD-9/10-CM code for schizophrenia (295.XX, F20.XX, or F21) during the study period (January 2008 to 12 months after the index date), with at least one of these visits occurring prior to the index date. Patients were also required to have received active care, defined as having at least one all-cause healthcare visit every 6 months within the system, during 12 months prior to (baseline period) and 12 months after (follow-up period) the index date, and at least one prescription for an oral antipsychotic medication during the baseline period. Patients with an administration of any other LAI prior to the index date, those with a prescription for clozapine during the baseline or follow-up period, and those with a diagnosis of bipolar disorder at any time during the study period (January 2008 to the end of the follow-up period) were excluded.

The analyses were repeated in a subgroup of patients with prior schizophrenia relapse. Patients included in this subgroup analysis, additionally, had at least one schizophrenia relapse at baseline, defined as a schizophrenia-related (with an associated ICD-9/10-CM diagnosis code for schizophrenia) hospitalization or ER visit.

Measures

Demographics (age, gender, and race/ethnicity), health insurance, and comorbidities were assessed during the baseline period. Age on the index date was reported as a continuous variable. Health insurance was determined considering the patient's payer for their healthcare visit on the index date. Comorbidities were determined on the basis of ICD-9-CM/ICD-10-CM diagnosis codes associated with the patients' healthcare visits during the baseline period. The number and proportion of patients with diabetes, hypertension, hyperlipidemia, cardiovascular conditions, respiratory conditions, neurological conditions, musculoskeletal conditions, and other mental health comorbidities (common comorbidities observed in patients with schizophrenia) were reported. In terms of mental health comorbidities, the number and proportion of patients with a

cognitive disorder (dementia, delirium, or amnesia), a psychotic disorder other than schizophrenia (delusional disorder or acute or transient psychotic disorder), an affective disorder (depression or bipolar and related disorder), anxiety, stress-related or somatoform disorder, a mental disorder associated with physical or physiological disturbances, a substance use disorder, a developmental disorder or a disorder diagnosed in childhood, and an unspecified disorder were reported (see Appendix 1 in the supplementary material). Also, the Elixhauser comorbidity index (ECI) was reported on the basis of the ICD-9-CM/ICD-10-CM diagnosis codes associated with the patients' healthcare visits during the baseline period.

All-cause, mental health-related (with an associated ICD-9-CM/ICD-10-CM diagnosis code for a mental health condition, Appendix 1 in the supplementary material), and schizophrenia-related inpatient, 7- and 30-day readmissions, ER, and outpatient visits were compared within the same cohort during the 12-month pre- and post-index periods. The proportion of patients with each type of visit and the mean number of visits were compared.

Data Analytic Procedures

Means, medians, interquartile ranges, and standard deviations were reported for continuous variables, and frequencies and percentages were reported for categorical variables. Findings were reported for the overall study cohort and separately for the subgroup with prior relapse at baseline. Comparisons of HRU measures during the 12-month pre- and post-index periods were performed using McNemar's and Wilcoxon signed-rank tests. All analyses were conducted using SAS version 9.4 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Sociodemographic and Clinical Characteristics

Figure 1 presents the number of patients satisfying the inclusion and exclusion criteria. The overall study cohort consisted of 210 patients. Of the total, 69.5% were male, 73.8% were black, and 39.1% had Medicaid. The mean age of the cohort was 34.2 (\pm 13.5) years and the mean ECI was 2.5 (\pm 1.6). All patients had at least one other mental comorbidity. Anxiety, stress-related, and somatoform disorders (95.2%), substance use disorders (68.1%), and psychotic disorders other than schizophrenia (61.9%) were the most common comorbid mental illnesses with 89.5% of the patients having more than one comorbid mental illness. Musculoskeletal conditions (29.5%), hypertension (28.6%), and hyperlipidemia (25.7%) were among the most common physical comorbidities (Table 1).

Of the 210 patients included in the overall study cohort, 157 (74.8%) had at least one relapse during the baseline period. Of these, 70.7% were male, 73.9% were black, and 41.4% had Medicaid. The mean age of the cohort was 33.6 (\pm 13.1) years and the mean ECI was 2.6 (\pm 1.6). Similar to the overall cohort, all patients had at least one other mental comorbidity and 91.8% had more than one. The most common mental and physical comorbidities were comparable with the overall cohort (Table 1).

HRU During 12-Month Pre- Vs. Post-Index Periods

All-Cause HRU

In the overall study cohort, from the pre- to post-index period, the proportion of patients with visits significantly decreased for all-cause inpatient visits (67.6% to 22.4%, $P < 0.001$), 7-day readmissions (5.2% to 1.0%, $P = 0.013$), 30-day readmissions (12.4% to 2.4%, $P < 0.001$), and ER visits (68.6% to 45.7%, $P < 0.001$). The mean number of visits reduced for inpatient visits (1.2 ± 1.2 to 0.4 ± 1.0 ,

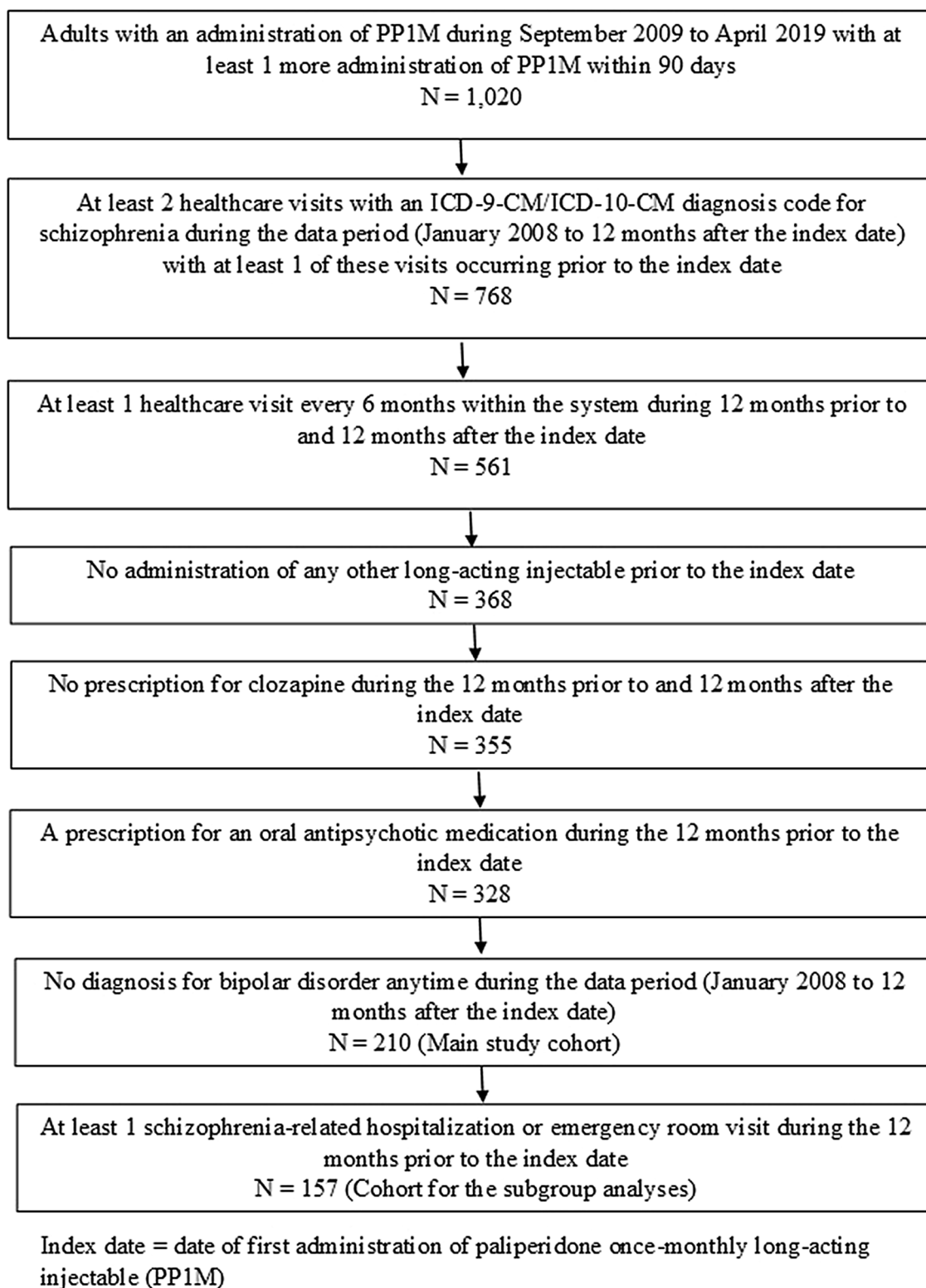


Fig. 1 Patient selection criteria

Table 1 Baseline demographic and clinical characteristics

Characteristics	All patients <i>n</i> = 210	Patients with ≥ 1 relapse ^a <i>n</i> = 157 (74.8%)
Age, mean \pm SD (median, IQR), years	34.2 \pm 13.5 (29.5, 20.0)	33.6 \pm 13.1 (29.0, 17.0)
Gender, <i>n</i> (%)		
Male	146 (69.5)	111 (70.7)
Female	64 (30.5)	46 (29.3)
Race/ethnicity, <i>n</i> (%)		
Non-Hispanic white	30 (14.3)	24 (15.3)
Non-Hispanic black	155 (73.8)	116 (73.9)
Hispanic	12 (5.7)	9 (5.7)
Unknown	13 (6.2)	8 (5.1)
Insurance, <i>n</i> (%)		
Commercial	16 (7.6)	11 (7.0)
Medicare	50 (23.8)	36 (22.9)
Medicaid	82 (39.1)	65 (41.4)
Self-pay	31 (14.8)	24 (15.3)
Other (charity and unknown)	31 (14.8)	21 (13.4)
Elixhauser comorbidity index, mean \pm SD (median, IQR)	2.5 \pm 1.6 (2.0, 2.0)	2.6 \pm 1.6 (3.0, 2.0)
Comorbidities, <i>n</i> (%)		
Other mental health conditions	210 (100.0)	157 (100.0)
Cognitive disorder	10 (4.5)	7 (4.5)
Psychotic disorder other than schizophrenia	130 (61.9)	98 (62.4)
Affective disorder	79 (37.2)	58 (36.9)
Anxiety, stress-related, or somatoform disorder	200 (95.2)	147 (93.6)
Personality disorder	29 (13.8)	23 (14.7)
Disorder associated with physical or physiological disturbances	73 (34.8)	60 (38.2)
Substance use disorder	143 (68.1)	116 (73.9)
Developmental disorder or disorder diagnosed in childhood	32 (15.2)	20 (12.7)
Unspecified disorder	3 (1.4)	1 (0.6)
> 1 type of mental comorbidity	188 (89.5)	144 (91.8)
Diabetes	29 (13.8)	21 (13.4)
Hypertension	60 (28.6)	47 (29.9)
Hyperlipidemia	54 (25.7)	39 (24.8)
Cardiovascular	28 (13.3)	22 (14.0)

Table 1 continued

Characteristics	All patients <i>n</i> = 210	Patients with ≥ 1 relapse ^a <i>n</i> = 157 (74.8%)
Musculoskeletal disorder	62 (29.5)	49 (31.2)

IQR interquartile range, *SD* standard deviation

^a Relapse defined as a schizophrenia-related inpatient or emergency room visit during the 12 months before PP1M initiation

$P < 0.001$), 7-day readmissions (0.1 ± 0.3 to 0.0 ± 0.1 , $P = 0.02$), 30-day readmissions (0.2 ± 0.5 to 0.1 ± 0.5 , $P = 0.002$), and ER visits (2.3 ± 3.2 to 1.2 ± 2.3 , $P < 0.001$) and the mean length of inpatient stay also reduced significantly (14.2 ± 16.8 to 4.4 ± 13.2 days, $P < 0.001$) from the pre- to post-index period. The mean number of all-cause outpatient visits increased (8.7 ± 5.5 to 11.6 ± 6.6 , $P < 0.001$) from the pre- to post-index period (Table 2).

In the subgroup of patients with prior relapse at baseline, from the pre- to post-index period, the proportion of patients with visits significantly decreased for all-cause inpatient visits (83.4% to 25.5%, $P < 0.001$), 7-day readmissions (7.0% to 0.6%, $P = 0.004$), 30-day readmissions (15.9% to 1.9%, $P < 0.001$), and ER visits (80.3% to 50.3%, $P < 0.001$). The mean number of visits reduced for inpatient visits (1.5 ± 1.2 to 0.5 ± 1.1 , $P < 0.001$), 7-day readmissions (0.1 ± 0.3 to 0.0 ± 0.1 , $P = 0.02$), 30-day readmissions (0.2 ± 0.6 to 0.1 ± 0.5 , $P = 0.002$), and ER visits (2.8 ± 3.5 to 1.4 ± 2.5 , $P < 0.001$), and the mean length of inpatient stay also reduced significantly (17.7 ± 16.6 to 5.3 ± 14.6 days, $P < 0.001$) from the pre- to post-index period. The mean number of all-cause outpatient visits increased (8.2 ± 5.2 to 10.8 ± 6.1 , $P < 0.001$) from the pre- to post-index period (Table 3).

Mental Health-Related HRU

In the overall study cohort, from the pre- to post-index period, the proportion of patients with visits significantly decreased for mental health-related inpatient visits (67.6% to 22.4%, $P < 0.001$), 7-day readmissions (5.2% to 1.0%,

$P = 0.013$), 30-day readmissions (12.4% to 2.4%, $P < 0.001$), and ER visits (57.6% to 33.3%, $P < 0.001$). The mean number of visits reduced for inpatient visits (1.2 ± 1.2 to 0.4 ± 1.0 , $P < 0.001$), 7-day readmissions (0.1 ± 0.3 to 0.0 ± 0.1 , $P = 0.02$), 30-day readmissions (0.2 ± 0.5 to 0.1 ± 0.5 , $P = 0.002$), and ER visits (1.5 ± 2.2 to 0.7 ± 1.4 , $P < 0.001$) and the mean length of inpatient stay also reduced significantly (14.2 ± 16.8 to 4.4 ± 13.2 days, $P < 0.001$) from the pre- to post-index period. The mean number of mental health-related outpatient visits increased (6.8 ± 4.6 to 10.6 ± 5.9 , $P < 0.001$) from the pre- to post-index period (Table 2).

In the subgroup of patients with prior relapse at baseline, from the pre- to post-index period, the proportion of patients with visits significantly decreased for mental health-related inpatient visits (83.4% to 25.5%, $P < 0.001$), 7-day readmissions (7.0% to 0.6%, $P = 0.004$), 30-day readmissions (15.9% to 1.9%, $P < 0.001$), and ER visits (72.6% to 35.7%, $P < 0.001$). The mean number of visits reduced for inpatient visits (1.5 ± 1.2 to 0.5 ± 1.1 , $P < 0.001$), 7-day readmissions (0.1 ± 0.3 to 0.0 ± 0.1 , $P = 0.02$), 30-day readmissions (0.2 ± 0.6 to 0.1 ± 0.5 , $P = 0.002$), and ER visits (2.0 ± 2.4 to 0.8 ± 1.6 , $P < 0.001$), and the mean length of inpatient stay also reduced significantly (17.7 ± 16.6 to 5.3 ± 14.6 days, $P < 0.001$) from the pre- to post-index period. The mean number of mental health-related outpatient visits increased (6.3 ± 4.2 to 9.8 ± 5.2 , $P < 0.001$) from the pre- to post-index period (Table 3).

Table 2 Healthcare resource utilization in the 12-month pre- and post-index periods in all patients ($N = 210$)

Measures	All-cause HRU			Mental health-related HRU			Schizophrenia-related HRU		
	12 months before initiation	12 months after initiation	<i>P</i> value	12 months before initiation	12 months after initiation	<i>P</i> value	12 months before initiation	12 months after initiation	<i>P</i> value
Inpatient visits and related measures									
Patients with inpatient visits, <i>n</i> (%)	142 (67.6)	47 (22.4)	< 0.001	142 (67.6)	47 (22.4)	< 0.001	129 (61.4)	43 (20.5)	< 0.001
Number of inpatient visits, mean \pm SD (median, IQR)	1.2 \pm 1.2 (1.0, 2.0)	0.4 \pm 1.0 (0.0, 0.0)	< 0.001	1.2 \pm 1.2 (1.0, 2.0)	0.4 \pm 1.0 (0.0, 0.0)	< 0.001	0.9 \pm 0.9 (1.0, 1.0)	0.3 \pm 0.8 (0.0, 0.0)	< 0.001
Patients with 7-day readmissions, <i>n</i> (%)	11 (5.2)	2 (1.0)	0.013	11 (5.2)	2 (1.0)	0.013	8 (3.8)	2 (1.0)	0.16
Number of 7-day readmissions, mean \pm SD (median, IQR)	0.1 \pm 0.3 (0.0, 0.0)	0.0 \pm 0.1 (0.0, 0.0)	0.02	0.1 \pm 0.3 (0.0, 0.0)	0.0 \pm 0.1 (0.0, 0.0)	0.02	0.0 \pm 0.2 (0.0, 0.0)	0.0 \pm 0.1 (0.0, 0.0)	0.058
Patients with 30-day readmissions, <i>n</i> (%)	26 (12.4)	5 (2.4)	< 0.001	26 (12.4)	5 (2.4)	< 0.001	18 (8.6)	3 (1.4)	0.001
Number of 30-day readmissions, mean \pm SD (median, IQR)	0.2 \pm 0.5 (0.0, 0.0)	0.1 \pm 0.5 (0.0, 0.0)	0.002	0.2 \pm 0.5 (0.0, 0.0)	0.1 \pm 0.5 (0.0, 0.0)	0.002	0.1 \pm 0.3 (0.0, 0.0)	0.0 \pm 0.3 (0.0, 0.0)	0.010
Length of stay, mean \pm SD (median, IQR), days	14.2 \pm 16.8 (10.0, 22.0)	4.4 \pm 13.2 (0.0, 0.0)	< 0.001	14.2 \pm 16.8 (10.0, 22.0)	4.4 \pm 13.2 (0.0, 0.0)	< 0.001	11.9 \pm 14.9 (8.5, 19.0)	3.5 \pm 10.5 (0.0, 0.0)	< 0.001
Outpatient visits									
Patients with outpatient visits, <i>n</i> (%)	208 (99)	206 (98.1)	0.414	204 (97.1)	204 (97.1)	0.999	184 (87.6)	192 (91.4)	0.074
Number of outpatient visits, mean \pm SD (median, IQR)	8.7 \pm 5.5 (8.0, 6.0)	11.6 \pm 6.6 (11.0, 5.0)	< 0.001	6.8 \pm 4.6 (6.0, 7.0)	10.6 \pm 5.9 (11.0, 4.0)	< 0.001	4.6 \pm 3.9 (3.0, 7.0)	8.4 \pm 5.3 (9.0, 6.0)	< 0.001

Table 2 continued

Measures	All-cause HRU			Mental health-related HRU			Schizophrenia-related HRU		
	12 months before initiation	12 months after initiation	P value	12 months before initiation	12 months after initiation	P value	12 months before initiation	12 months after initiation	P value
Emergency room visits									
Patients with emergency room visits, <i>n</i> (%)	144 (68.6)	96 (45.7)	< 0.001	121 (57.6)	70 (33.3)	< 0.001	88 (41.9)	58 (27.6)	0.001
Number of emergency room visits, mean ± SD (median, IQR)	2.3 ± 3.2 (2.0, 3.0)	1.2 ± 2.3 (0.0, 1.0)	< 0.001	1.5 ± 2.2 (1.0, 2.0)	0.7 ± 1.4 (0.0, 1.0)	< 0.001	0.9 ± 1.5 (0.0, 1.0)	0.5 ± 1.1 (0.0, 1.0)	< 0.001

HRU health resource utilization, IQR interquartile range, SD standard deviation

Schizophrenia-Related HRU

In the overall study cohort, from the pre- to post-index period, the proportion of patients with visits significantly decreased for schizophrenia-related inpatient visits (61.4% to 20.5%, *P* < 0.001), 30-day readmissions (8.6% to 1.4%, *P* = 0.001), and ER visits (41.9% to 27.6%, *P* = 0.001). The mean number of visits reduced for inpatient visits (0.9 ± 0.9 to 0.3 ± 0.8, *P* < 0.001), 30-day readmissions (0.1 ± 0.3 to 0.0 ± 0.3, *P* = 0.01), and ER visits (0.9 ± 1.5 to 0.5 ± 1.1, *P* < 0.001), and the mean length of inpatient stay also reduced significantly (11.9 ± 14.9 to 3.5 ± 10.5 days, *P* < 0.001) from the pre- to post-index period. The mean number of schizophrenia-related outpatient visits increased (4.6 ± 3.9 to 8.4 ± 5.3, *P* < 0.001) from the pre- to post-index period (Table 2).

In the subgroup of patients with prior relapse at baseline, from the pre- to post-index period, the proportion of patients with visits significantly decreased for schizophrenia-related inpatient visits (82.2% to 24.2%, *P* < 0.001), 7-day readmissions (5.1% to 0.6%, *P* = 0.009), 30-day readmissions (11.5% to 1.3%, *P* < 0.001), and ER visits (56.1% to 30.6%, *P* < 0.001). The mean number of visits reduced for inpatient visits (1.2 ± 0.9 to 0.4 ± 0.9, *P* < 0.001), 7-day readmissions (0.1 ± 0.2 to 0.0 ± 0.1, *P* = 0.039), 30-day readmissions (0.1 ± 0.3 to 0.0 ± 0.4, *P* < 0.001), and ER visits (1.2 ± 1.6 to 0.6 ± 1.2, *P* < 0.001), and the mean length of inpatient stay also reduced significantly (16.0 ± 15.2 to 4.5 ± 12.0 days, *P* < 0.001) from the pre- to post-index period. The mean number of schizophrenia-related outpatient visits increased (4.4 ± 3.7 to 8.3 ± 5.2, *P* < 0.001) from the pre- to post-index period (Table 3).

DISCUSSION

This retrospective cohort study examined the HRU during 12 months before and after the initiation of PP1M in patients with schizophrenia receiving care at an integrated healthcare system in the USA. In terms of characteristics of the study cohort, similar to previous reports

Table 3 Healthcare resource utilization in the 12-month pre- and post-index periods in patients with prior relapse ($N = 157$)

Measures	All-cause HRU			Mental health-related HRU			Schizophrenia-related HRU		
	12 months before initiation	12 months after initiation	<i>P</i> value	12 months before initiation	12 months after initiation	<i>P</i> value	12 months before initiation	12 months after initiation	<i>P</i> value
Inpatient visits and related measures									
Patients with inpatient visits, <i>n</i> (%)	131 (83.4)	40 (25.5)	< 0.001	131 (83.4)	40 (25.5)	< 0.001	129 (82.2)	38 (24.2)	< 0.001
Number of inpatient visits, mean \pm SD (median, IQR)	1.5 \pm 1.2 (1.0, 1.0)	0.5 \pm 1.1 (0.0, 1.0)	< 0.001	1.5 \pm 1.2 (1.0, 1.0)	0.5 \pm 1.1 (0.0, 1.0)	< 0.001	1.2 \pm 0.9 (1.0, 1.0)	0.4 \pm 0.9 (0.0, 0.0)	< 0.001
Patients with 7-day readmissions, <i>n</i> (%)	11 (7.0)	1 (0.6)	0.004	11 (7.0)	1 (0.6)	0.004	8 (5.1)	1 (0.6)	0.009
Number of 7-day readmissions, mean \pm SD (median, IQR)	0.1 \pm 0.3 (0.0, 0.0)	0.0 \pm 0.1 (0.0, 0.0)	0.020	0.1 \pm 0.3 (0.0, 0.0)	0.0 \pm 0.1 (0.0, 0.0)	0.020	0.1 \pm 0.2 (0.0, 0.0)	0.0 \pm 0.1 (0.0, 0.0)	0.039
Patients with 30-day readmissions, <i>n</i> (%)	25 (15.9)	3 (1.9)	< 0.001	25 (15.9)	3 (1.9)	< 0.001	18 (11.5)	2 (1.3)	< 0.001
Number of 30-day readmissions, mean \pm SD (median, IQR)	0.2 \pm 0.6 (0.0, 0.0)	0.1 \pm 0.5 (0.0, 0.0)	0.002	0.2 \pm 0.6 (0.0, 0.0)	0.1 \pm 0.5 (0.0, 0.0)	0.002	0.1 \pm 0.3 (0.0, 0.0)	0.0 \pm 0.4 (0.0, 0.0)	< 0.001
Length of stay (days), mean \pm SD (median, IQR)	17.7 \pm 16.6 (13.0, 18.0)	5.3 \pm 14.6 (0.0, 1.0)	< 0.001	17.7 \pm 16.6 (13.0, 18.0)	5.3 \pm 14.6 (0.0, 1.0)	< 0.001	16.0 \pm 15.2 (12.0, 16.0)	4.5 \pm 12.0 (0.0, 0.0)	< 0.001
Outpatient visits									
Patients with outpatient visits, <i>n</i> (%)	155 (98.7)	153 (97.5)	0.414	151 (96.2)	152 (96.8)	0.706	137 (87.3)	145 (92.4)	0.046
Number of outpatient visits, <i>n</i> (%)	8.2 \pm 5.2 (7.0, 6.0)	10.8 \pm 6.1 (11.0, 5.0)	< 0.001	6.3 \pm 4.2 (6.0, 6.0)	9.8 \pm 5.2 (10.0, 5.0)	< 0.001	4.4 \pm 3.7 (3.0, 6.0)	8.3 \pm 5.2 (9.0, 6.0)	< 0.001

Table 3 continued

Measures	All-cause HRU			Mental health-related HRU			Schizophrenia-related HRU		
	12 months before initiation	12 months after initiation	P value	12 months before initiation	12 months after initiation	P value	12 months before initiation	12 months after initiation	P value
Emergency room visits									
Patients with emergency room visits, <i>n</i> (%)	126 (80.3)	79 (50.3)	< 0.001	114 (72.6)	56 (35.7)	< 0.001	88 (56.1)	48 (30.6)	0.001
Number of emergency room visits, mean ± SD (median, IQR)	2.8 ± 3.5 (2.0, 2.0)	1.4 ± 2.5 (1.0, 2.0)	< 0.001	2.0 ± 2.4 (1.0, 2.0)	0.8 ± 1.6 (0.0, 1.0)	< 0.001	1.2 ± 1.6 (1.0, 2.0)	0.6 ± 1.2 (0.0, 1.0)	< 0.001

HRU health resource utilization, IQR interquartile range, SD standard deviation

[36, 37], the majority of the patients initiated on PP1M were male and non-Hispanic black, possibly because of the higher risk of antipsychotic non-adherence in these patients [13, 38]. The results showed that initiation of PP1M was associated with a reduction in acute HRU (inpatient and ER use) in the overall study cohort as well as the subset of patients with prior relapse. The reduction in acute HRU after PP1M initiation is likely to be due to better control of schizophrenia symptoms associated with improvement in medication adherence compared to previous treatment with oral antipsychotics. In addition to reduction in schizophrenia-related psychotic events requiring an ER visit and/or hospitalization, better control of schizophrenia symptoms also likely positively impacts self-management behaviors with regard to physical and mental comorbidities common in these patients, thereby leading to improvement in overall physical and mental health and, in turn, reduction in mental health-related and all-cause acute healthcare use [39]. Our findings are consistent with previous similar studies on this topic [29–31]. For example, in a previous study of Veteran Affairs patients transitioning from orally administered paliperidone/risperidone to PP1M, Patel et al. found that the mean number of visits reduced for all-cause (2.3 to 1.5, $p < 0.05$), mental health-related (1.5 to 0.8, $p < 0.05$), and schizophrenia-related inpatient visits (0.6 to 0.3, $p < 0.05$) from 12 months before to 12 months after transitioning to PP1M. The mean length of stay also reduced for all-cause (28.1 to 14.0 days, $p < 0.05$), mental health-related (27.1 to 13.8 days, $p < 0.05$), and schizophrenia-related (13.2 to 5.7 days, $p < 0.05$) inpatient visits [30]. Other studies have compared HRU between patients on PP1M and those on oral antipsychotics and have reported reduced acute HRU in patients on PP1M compared to those on oral antipsychotics [23–28]. Manjeliavskaia et al. studied multistate Medicaid beneficiaries with schizophrenia and found lower proportions of patients with all-cause inpatient visits (25.6% vs. 33.9%, $p < 0.001$) and ER visits (54.7% vs. 65.8%, $p < 0.001$) during the 12 months after initiation

of PP1M compared to patients initiated on oral antipsychotics [27].

As expected and consistent with the previous studies [24, 30], the mean number of outpatient visits increased significantly from pre to post PP1M initiation. PP1M treatment necessitates a physician outpatient visit each month as opposed to oral antipsychotic treatment in which routine visits are usually spaced every 3–6 months. The increase in the frequency of outpatient visits along with PP1M administration costs adds to the routine schizophrenia treatment costs in patients with PP1M. However, it has been reported that the increase in routine schizophrenia treatment costs in patients on PP1M is offset by the reduction in total costs due to reduced acute care utilization [23, 29, 31]. Taken together, our findings combined with those from other similar studies indicate that clinical and economic benefits are associated with PP1M.

The extent of reduction in the rates of acute HRU after PP1M initiation was higher in the subgroup of patients with prior schizophrenia relapse during the baseline period compared to the overall study cohort. For example, the proportion of patients with schizophrenia-related 30-day readmissions reduced nearly 89% from the pre- to post-index period, from 11.5% to 1.3%, in patients with prior relapse compared to about an 83% reduction from 8.6% to 1.4% in the overall cohort. The mean number of mental health-related ER visits decreased 60% from the pre- to post-index period, from 2.0 to 0.8, in patients with prior relapse compared to an approximately 53% reduction from 1.5 to 0.7 in the overall cohort. While the direct comparison of the findings between patients with and without a relapse was beyond the scope of this study, the higher relative reduction in acute HRU after PP1M initiation in patients with a relapse during the baseline period suggests that the use of PP1M could be particularly beneficial in patients with a recent relapse, who are likely to be highly non-adherent to their oral antipsychotic regimen.

Despite the likely clinical and economic benefits, the use of PP1M and other LAIs remains low in patients with schizophrenia with prescription rates less than 20% [40]. In a

multisite nationwide observational study conducted in the USA, only about 12% of the patients who were non-adherent on oral antipsychotics were prescribed an LAI [41]. Patient factors such as feeling of coerciveness and/or stigma, high cost, and inconvenience due to the need to travel to the clinician's office; physician factors such as limited knowledge and experience with LAIs, personal bias against the use of needles, and increase in workload associated with the start of a new treatment; and health system factors such as requirement of prior authorization from payors and the need for large amount of resources (budget, storage, and staff) have been reported to be the barriers to LAI use [42–45]. Some of the proposed solutions to overcome these barriers include introduction of LAIs early in the treatment course, psychological interventions to address the fear of needles, shared decision-making approach with provision of accurate and updated information to the patients, provision of better education regarding LAIs during training and residency, and easier access from the insurance companies [43–45]. These approaches should be implemented in routine clinical practice to increase the use of PP1M and other LAIs in appropriate patients.

There are a few limitations in this study. Data entry errors are possible in the EMRs and hence there could be inaccuracies. Prior use of oral antipsychotics was determined on the basis of prescription orders written by the physicians, not on the actual use of the medication. Also, while the inclusion criterion of one healthcare visit within the system every 6 months during the study period maximized the likelihood that patients were not lost to follow-up, it is possible that some patients completed some but not all visits within the system. Mirror-image studies are prone to expectation bias, which occurs as a result of patients'/providers' expectations of a certain outcome when a new treatment is started [46]. Comparative analyses involving a control group of patients on oral antipsychotics were not conducted because of the difficulty in identifying a control group comparable in characteristics. Prior analyses conducted by some of the authors of the study suggested that patients initiated on PP1M usually have more

severe schizophrenia and are usually less adherent to their oral antipsychotic regimen prior to PP1M initiation compared to patients who stay on oral antipsychotics. Also, imbalance between the groups is possible because of differences in factors such as family and social support, neighborhood disadvantage, employment, and lifestyle behaviors including exercise, diet, smoking, and alcohol use, information regarding which is not available in the EMRs. Therefore, a pre–post one-group study design, in which patients act as their own controls, was deemed appropriate for this study. A limitation of this study design is that it does not account for variation in patient characteristics over time. However, it could be expected that major changes in patient characteristics would not have occurred during the observation period of 24 months in this study. The impact of antipsychotic polypharmacy prior to and during PP1M use on the study outcomes was not examined as part of this study. Data on important outcomes in patients with schizophrenia such as symptom severity, cognition, quality of life, and treatment-emergent adverse events were not available. Finally, the findings of this study were from one healthcare system in the southeastern USA, primarily North Carolina, and therefore the findings may not be generalizable to other settings.

CONCLUSIONS

Initiation of PP1M was associated with reduced acute healthcare use in patients with schizophrenia receiving care at an integrated healthcare system, indicating possible clinical and economic benefits of the medication. A more substantial reduction in acute HRU was observed in patients with a prior relapse compared with the overall cohort. Initiation of PP1M may be particularly beneficial in these patients. Our findings complement the findings from previous studies using data from certain payers and/or specific healthcare settings. Strategies aimed at removing barriers to use of LAIs like PP1M in eligible patients should be implemented in clinical practice. Future studies could examine treatment continuity and health

outcomes in patients initiated on PP1M transitioning between settings (e.g., post-discharge) or during unexpected events (e.g., COVID-19).

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Compliance with Ethics Guidelines. This study protocol was approved by Advarra Institutional Review Board (Reference Number Pro00034063). This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available as Atrium Health privacy policies do not allow sharing data with Atrium Health patient information in

order to comply with the Health Information Portability and Accountability Act.

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