Impact of Paliperidone Palmitate Versus Oral Atypical Antipsychotics on Health Care Resource Use and Costs in Veterans With Schizophrenia

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ABSTRACT

Objective: To compare health care resource utilization and costs in veterans with schizophrenia treated with paliperidone palmitate (PP) versus oral atypical antipsychotics (OAAs).

Methods: A retrospective longitudinal study was conducted using electronic health record data from the Veterans Health Administration. Veterans with schizophrenia (identified using *ICD-9-CM* 295.x) initiating PP or OAAs between January 2010 and October 2014, with ≥ 12 months of benefits enrollment prior to treatment initiation and ≥ 6 months of enrollment after treatment initiation, and with ≥ 1 Global Assessment of Functioning measurement at baseline were included. Inverse probability of treatment weighted regression models were used to estimate incidence rate ratios (IRRs) and cost differences (CDs) for the impact of PP versus OAAs on health care resource utilization and costs.

Results: Among 10,290 eligible veterans, 2,285 and 8,005 were initiated on PP and OAAs, respectively. After adjustment, PP was associated with less frequent all-cause inpatient hospitalizations (IRR = 0.89, $P < .001$) and more frequent mental health intensive case management visits (IRR = 1.81, $P < .001$) compared to OAAs. PP treatment was associated with higher likelihood of increased income (odds ratio [OR] = 1.20, $P = .027$) and lower likelihood of homelessness (OR = 0.82, $P < .001$). While mean annual pharmacy and outpatient costs were higher among PP users (CD = $3,417 pharmacy, $2,527 outpatient, $P < .001$), mean annual inpatient costs were lower (CD = –$14,456, $P < .001$), resulting in average annual total health care (medical and pharmacy) cost savings associated with PP (CD = –$8,511, $P = .012$) relative to OAAs.

Conclusions: PP treatment was associated with significantly lower total health care costs attributable to reduced inpatient admissions compared to OAAs. Higher mental health intensive case management participation among PP users may have contributed to the differences observed.

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Schizophrenia is a chronic mental illness that limits patients' capacity for self-care, employment, and maintaining personal relationships.[1] A systematic review estimated the incidence of schizophrenia to be about 15.2 per 100,000 persons in the United States, with an annual cost of approximately $30,000 per patient.[2]

As the largest integrated health care system in the United States, the Veterans Health Administration (VHA) cares for more than 6.9 million veterans annually, providing integrated and comprehensive services including primary, specialty, and inpatient care, rehabilitation services, long-term and home care, and other services to US military veterans.[3] The number of veterans dealing with mental health issues has increased over time, and veterans with schizophrenia occupy more hospital beds than veterans with any other illness.[4–6]

When treating schizophrenia with oral antipsychotics, nonadherence often undermines the effectiveness of pharmacotherapy.[7] Long-acting injectable antipsychotic therapies (LATs) are administered less frequently, thus providing extended medication coverage, which may improve adherence.[8] Among injectable antipsychotics, paliperidone palmitate (PP) is an atypical LAT dosed monthly and approved by the US Food and Drug Administration (FDA) in 2009 for acute and maintenance treatment of schizophrenia. PP has demonstrated effectiveness for treating schizophrenia, though the drug cost is greater than that of oral atypical antipsychotics (OAAs).[9–11] While some meta-analyses of randomized controlled trials (RCTs) comparing LATs to oral antipsychotics found no significant difference in clinical outcomes of patients receiving either treatment, the controlled environment of RCTs may not accurately reflect routine practice and real-world outcomes among schizophrenia patients.[12,13] For instance, RCTs may enroll patients who are more likely to be adherent to their prescribed treatment regimens or have less severe disease.[13] Requiring regular follow-up in RCTs may also increase adherence to prescribed regimens.

The objective of this study was to compare treatment patterns, health care resource utilization (HRU), and economic outcomes in US veterans treated with PP versus OAAs.

METHODS

Study Design and Patient Selection

A retrospective longitudinal cohort study was conducted using electronic medical record data from the VHA. The VHA Corporate Data Warehouse is an integrated and unified medical record system that contains data from all outpatient visits, hospital stays, treatments, prescriptions, laboratory results, billing, benefits information, demographics, socioeconomic information, and estimated costs of hospital stays and health care encounters.

Clinical Points

- Few real-world observational studies have compared health care cost and resource use outcomes associated with paliperidone palmitate and oral atypical antipsychotics.
- Although higher mental health intensive case management participation among patients treated with paliperidone palmitate may be a contributing factor, treatment with this medication was associated with significantly lower total health care costs attributable to fewer hospitalizations compared to oral atypical antipsychotics.

The study design scheme is presented in Supplementary eFigure 1. Since PP was approved by the FDA on July 21, 2009, the study observation period began on January 1, 2010, to allow for uptake of the drug. The study population included veterans 18 years or older who had at least 2 schizophrenia diagnoses (*ICD-9-CM* code 295.x) during the observation period (at least 1 of which occurred during the baseline period) and at least 2 dispensings of PP or OAA within 90 days between January 1, 2010, and October 31, 2014, the first of which defined the index date. Patients were also required to be enrolled with VA benefits at least 12 months before (ie, baseline) and 6 months after the index date, have at least 1 Global Assessment of Functioning (GAF)[14,15] measurement during baseline, and show evidence of at least 1 health care–related activity at least 6 months prior to the end of observation or a record of death. Patients receiving OAA were not allowed to have evidence of PP during the follow-up period but were still included in the study if they used other LATs during this period. Health care resource utilization and cost outcomes were assessed during the 12-month post-index period and annualized to 12 months for patients with less than 12 months of follow-up data.

Treatment, Outcomes, and Covariates

PP and OAAs were identified using NDC codes from inpatient and outpatient pharmacy and procedure records. The 9 OAAs included in the study were aripiprazole, asenapine maleate, iloperidone, lurasidone, olanzapine, quetiapine fumarate, risperidone, ziprasidone, and oral paliperidone.

Demographic, economic, and clinical characteristics were assessed during the 12-month pre-index baseline period including age, gender, race, region, marital status, homelessness, income, time since the availability of PP, Quan Charlson Comorbidity Index (CCI) score,[16–18] previous treatment with antipsychotics, concomitant medications, HRU, health care costs, physical comorbidities, mental health comorbidities, and GAF score. Income values were based on means-testing data, which is conducted periodically to determine whether veterans are eligible for care at no or reduced out-of-pocket costs due to lower incomes. Information about veterans' source of income was not available.

The outcomes of interest were treatment patterns, HRU, and health care costs. Treatment patterns assessed included days of persistence, proportion of patients with a gap in treatment from the date of dispensing plus days' supply greater than 30 or 60 days, proportion of days covered (PDC), antipsychotic use (other than the index drug), and concomitant medication use. Persistence was defined conservatively using the minimum number of days a patient was observed to receive treatment, allowing a maximum gap of 30 days following the date of dispensing plus days' supply. Proportion of days covered is defined as the proportion of days during the measurement period "covered" by prescription dispensings for the same medication. Antipsychotic polypharmacy was defined as having at least 60 consecutive days with overlapping coverage of at least 2 unique antipsychotic agents. Psychiatric polypharmacy was defined as having at least 60 consecutive days with overlapping coverage of at least 1 antipsychotic agent and at least 1 anxiolytic, antidepressant, or mood stabilizer. All-cause HRU and health care cost outcomes were annualized, assessed, and reported overall (ie, medical and pharmacy) and by type of services. Cost values were inflated to US $2014 using the Medical Services component of the Consumer Product Index.[19] VHA Decision Support System data were used to evaluate costs.

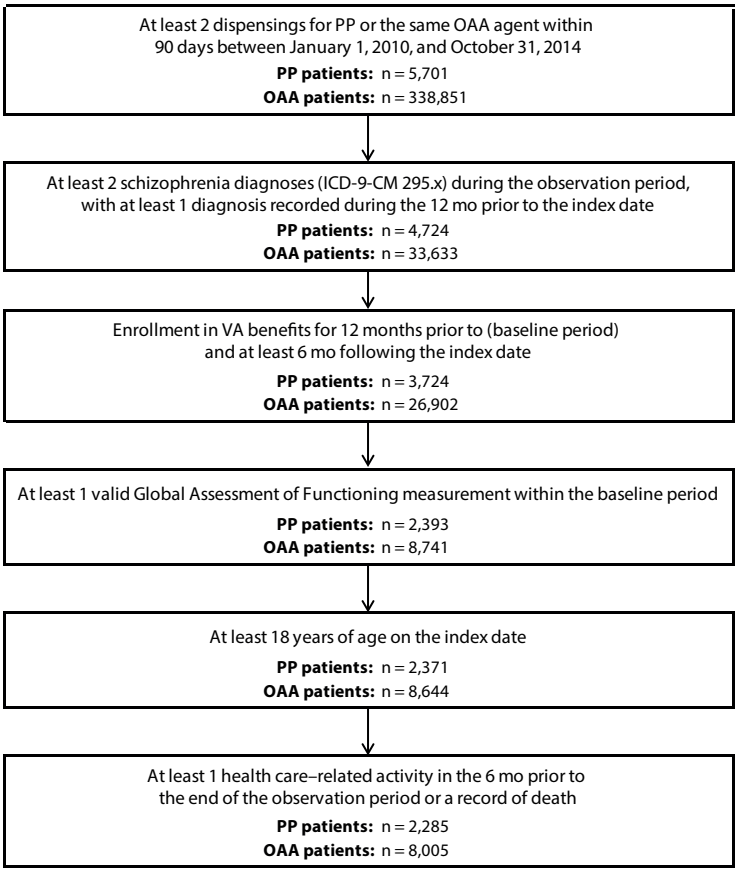
Statistical Analysis

Inverse probability of treatment weighting. Inverse probability of treatment weighting was used to adjust for baseline differences between PP and OAA patients. Inverse probability of treatment weights (IPTWs) are defined as the inverse of the conditional probability of receiving a patient's own treatment.[20] Applying the IPTW creates a pseudopopulation in which the distribution of baseline confounders used to create the weights is balanced between cohorts.[20,21]

IPTWs were calculated for each patient in the PP and OAA cohorts. The propensity score (PS) was calculated using a pooled logistic regression model adjusting for the following baseline variables: index year, age, gender, race, region, marital status, homelessness, income, number of mental health diagnoses, CCI, antipsychotic use, concomitant medication use, schizophrenia diagnoses, mental and physical comorbidities with greater than 10% prevalence in baseline, GAF score, and the number and cost of inpatient and outpatient visits. IPTWs were then constructed as 1/PS for the PP cohort and 1/(1 – PS) for the OAA cohort. Normalized IPTWs were calculated by dividing each IPTW by the overall mean IPTW, and were examined for extreme values.[22]

Descriptive analyses. Unadjusted and IPTW-weighted baseline patient characteristics, treatment patterns during the observation period, and HRU following a mental health inpatient visit were summarized and compared between the PP and OAA cohorts using χ^2 tests for categorical variables and Wilcoxon nonparametric tests for continuous variables. Imbalances in unadjusted and adjusted baseline covariates between the PP and OAA cohorts were assessed using standardized differences (std diff), with a threshold of > 10% indicating an imbalance.[23]

Figure 1. Sample Selection Criteria for Patients Using Oral Atypical Antipsychotics (OAA) and Paliperidone Palmitate (PP) in Veterans Affairs (VA) Data



Regression models. IPTW-weighted linear and Poisson regression models were used to estimate the mean cost difference (CD) and incidence rate ratios (IRRs) for the impact of PP versus OAA on health care costs and HRU. The weighted models included a binary indicator for the index treatment variable; linear regression models for cost outcomes also included an adjustment covariate for total baseline costs to account for residual confounding. A nonparametric bootstrap procedure was used to calculate confidence intervals and *P* values based on 499 resamples of the dataset for health care cost outcomes to account for nonnormality. No adjustment was made for multiplicity. All analyses were conducted in SAS version 9.4 (SAS Institute, Cary, NC).

Sensitivity analysis. A sensitivity analysis was conducted to assess whether mental health intensive case management (MHICM, a VA program similar to assertive community treatment[24] consisting of a multidisciplinary team of professionals using a client-centered, community-based approach to assist veterans with mental illness to live independently in the community) participation[25] modified the association between treatment and outcomes. All statistical analyses were repeated in subgroups stratified by MHICM participation at baseline.

In addition, weighted logistic regression models were used to assess the impact of PP versus OAA on an increase in income (a binary variable based on whether a veteran's income increased from baseline) and homelessness during the 12-month study period. Odds ratios, 95% confidence intervals, and *P* values were reported.

RESULTS

A total of 2,285 PP patients and 8,005 OAA patients were included in this study (Figure 1). Applying IPTW (weight range of 0.51–42.3, mean = 1.0, standard deviation = 1.67) to these treatment cohorts created a pseudopopulation of 5,052 PP patients and 5,238 OAA patients.

Baseline Demographic and Clinical Characteristics

Unadjusted and IPTW-adjusted baseline characteristics of the study population are reported in Table 1. Before adjustment, on average, PP patients were younger than OAA patients (mean age of 50.2 vs 53.7 years, std diff = 27.2%). The proportions of male OAA and PP patients appeared similar, though PP patients were more likely to be single and homeless compared to OAA patients (single: 46.8% vs 39.3%, std diff = 15.2%; homeless: 34.0% vs 29.0%, std diff = 10.6%). After applying IPTW, standardized differences greater than 10% were observed for only a few covariates, suggesting that the distribution of baseline confounders between the PP and OAA cohorts were balanced. Notably, PP patients were more likely to have received a greater number of unique antipsychotic agents (2.4 vs 1.3, std diff = 57.0%) than patients treated with OAAs. PP patients were also more likely to have used atypical oral and short-term injectable antipsychotics (87.6% vs 58.0%, std diff = 70.6%) and atypical LATs (33.5% vs 6.4%, std diff = 71.9%) than OAA patients.

Treatment Patterns During Follow-Up

Treatment patterns evaluated during the annualized 12-month study period (after PP or OAA initiation) are presented in Table 2. Compared to OAA patients, patients treated with PP were persistent for a longer mean duration of time (209.6 days vs 165.0 days, $P < .001$) and a lower proportion of PP patients had a treatment gap of at least 30 days or at least 60 days (71.2% vs 83.0%, $P < .001$ and 60.6% vs 74.0%, $P < .001$). A higher proportion of PP patients had PDC ≥ 0.8 for their index drug (35.8% vs 23.3%, $P < .001$) compared to their OAA counterparts. In addition, a lower proportion of PP patients had psychiatric polypharmacy during the observation period compared to OAA patients (40.3% vs 47.8%, $P < .001$).

Association Between Treatment and HRU

As shown in Table 3, treatment with PP was associated with a lower rate of inpatient stays (IRR = 0.89, $P < .001$) and days in an inpatient setting

Table 1. Baseline Characteristics of the Study Population

	Unadjusted			IPTW-Adjusted		
	PP Patients (n = 2,285)	OAA Patients (n = 8,005)	Standardized Difference (%)[a]	PP Patients (n = 5,052)	OAA Patients (n = 5,238)	Standardized Difference (%)[a]
Length of study period (years),[b] mean ± SD [median]	2.2 ± 1.1 [2.1]	3.0 ± 1.3 [3.2]	63.9†	2.7 ± 1.8 [2.8]	2.8 ± 1.1 [2.9]	8.1
Age at index date (years), mean ± SD [median]	50.2 ± 12.9 [53.0]	53.7 ± 12.0 [55.2]	27.7†	53.4 ± 17.2 [55.5]	53.0 ± 9.8 [54.8]	3.2
Gender, n (%)						
Male	2,054 (89.9)	7,258 (90.7)	2.6	4,529 (89.6)	4,742 (90.5)	3.0
Female	225 (9.8)	722 (9.0)	2.8	503 (10.0)	479 (9.1)	2.8
Unknown	6 (0.3)	25 (0.3)	0.9	20 (0.4)	16 (0.3)	1.4
Race, n (%)						
White	822 (36.0)	3,193 (39.9)	8.1	2,115 (41.9)	2,056 (39.3)	5.3
Hispanic, white	82 (3.6)	243 (3.0)	3.1	211 (4.2)	154 (2.9)	6.7
Black	518 (22.7)	2,007 (25.1)	5.6	1,310 (25.9)	1,292 (24.7)	2.9
Hispanic, black	8 (0.4)	22 (0.3)	1.4	19 (0.4)	13 (0.3)	2.0
Asian	10 (0.4)	27 (0.3)	1.6	51 (1.0)	19 (0.4)	7.8
Indian	7 (0.3)	21 (0.3)	0.8	16 (0.3)	15 (0.3)	0.8
Unknown	928 (40.6)	2,757 (34.4)	12.8†	1,560 (30.9)	1,855 (35.4)	9.7
US region, n (%)						
Northeast	343 (15.0)	1,302 (16.3)	3.5	864 (17.1)	849 (16.2)	2.4
Midwest	531 (23.2)	1,851 (23.1)	0.3	1,228 (24.3)	1,220 (23.3)	2.4
South	934 (40.9)	3,273 (40.9)	0.0	1,976 (39.1)	2,122 (40.5)	2.9
West	445 (19.5)	1,460 (18.2)	3.2	920 (18.2)	972 (18.6)	0.9
Other	29 (1.3)	108 (1.3)	0.7	42 (0.8)	67 (1.3)	4.3
Unknown	3 (0.1)	11 (0.1)	0.2	24 (0.5)	8 (0.1)	5.9
Marital status, n (%)						
Single	1,070 (46.8)	3,149 (39.3)	15.2†	2,216 (43.9)	2,159 (41.2)	5.4
Married	405 (17.7)	1,785 (22.3)	11.5†	991 (19.6)	1,112 (21.2)	4.0
Widowed	60 (2.6)	298 (3.7)	6.3	159 (3.2)	183 (3.5)	1.9
Divorced	749 (32.8)	2,759 (34.5)	3.6	1,683 (33.3)	1,776 (33.9)	1.3
Unknown	1 (0.0)	14 (0.2)	4.0	3 (0.1)	8 (0.1)	2.8
Homeless[c], n (%)	776 (34.0)	2,325 (29.0)	10.6†	1,436 (28.4)	1,567 (29.9)	3.3
Income[d] (US $2014), mean ± SD [median]	12,169.2 ± 13,394.9 [10,418.7]	12,312.7 ± 13,810.5 [10,008.7]	1.1	12,241.9 ± 19,383.8 [10,756.3]	12,211.0 ± 10,869.1 [10,158.2]	0.2
Time (years) since PP availability, mean ± SD [median]	3.0 ± 1.1 [3.0]	2.1 ± 1.2 [1.8]	76.2†	2.4 ± 1.8 [2.2]	2.3 ± 1.0 [2.1]	8.5
No. of unique mental health diagnoses, mean ± SD [median]	4.7 ± 1.9 [5.0]	4.8 ± 2.0 [5.0]	4.2	4.6 ± 2.8 [4.0]	4.8 ± 1.6 [5.0]	6.9
Quan CCI score, mean ± SD [median]	1.0 ± 1.5 [1.0]	1.3 ± 1.7 [1.0]	18.5†	1.3 ± 2.6 [1.0]	1.2 ± 1.3 [1.0]	2.0
PDC by any AP agent, n (%)						
PDC < 0.8	1,789 (78.3)	6,306 (78.8)	1.2	3,911 (77.4)	4,044 (77.2)	0.5
PDC ≥ 0.8	496 (21.7)	1,699 (21.2)	1.2	1,142 (22.6)	1,194 (22.8)	0.5
No. of unique AP agents received, mean ± SD [median]	2.7 ± 1.6 [2.0]	1.2 ± 1.2 [1.0]	106.2†	2.4 ± 2.4 [2.0]	1.3 ± 1.0 [1.0]	57.0†
AP use, n (%)						
Typical oral and short-term injectable APs	1,160 (50.8)	2,952 (36.9)	28.3†	2,193 (43.4)	2,115 (40.4)	6.1
Atypical oral and short-term injectable APs	2,205 (96.5)	4,501 (56.2)	107.7†	4,426 (87.6)	3,036 (58.0)	70.6†
Typical LAT	302 (13.2)	690 (8.6)	14.8†	628 (12.4)	498 (9.5)	9.4
Atypical LAT	607 (26.6)	486 (6.1)	57.7†	1,691 (33.5)	336 (6.4)	71.9†
Concomitant medication use[e], n (%)						
Antidepressant	1,447 (63.3)	5,089 (63.6)	0.5	3,258 (64.5)	3,261 (62.3)	4.6
Anxiolytics	1,806 (79.0)	5,636 (70.4)	20.0†	3,980 (78.8)	3,680 (70.3)	19.6†
Mood stabilizer	688 (30.1)	2,358 (29.5)	1.4	1,413 (28.0)	1,535 (29.3)	3.0
None of the above	210 (9.2)	456 (5.7)	13.3†	376 (7.4)	340 (6.5)	3.7
Polypharmacy						
AP polypharmacy,[f] n (%)	233 (10.2)	521 (6.5)	13.4†	553 (10.9)	373 (7.1)	13.4†
Length of AP polypharmacy (days), mean ± SD [median]	204.4 ± 83.8 [209.0]	232.6 ± 79.8 [248.0]	34.4†	212.7 ± 127.0 [215.0]	236.3 ± 67.4 [249.0]	23.2†
Psychiatric polypharmacy,[g] n (%)	764 (33.4)	2,552 (31.9)	3.3	1,608 (31.8)	1,747 (33.4)	3.3
Length of psychiatric polypharmacy (days), mean ± SD [median]	232.7 ± 79.1 [238.0]	251.0 ± 74.3 [268.0]	23.9†	234.0 ± 113.7 [237.0]	252.1 ± 61.4 [269.0]	19.8†
All-cause resource utilization						
No. of inpatient stays per patient, mean ± SD [median]	2.5 ± 2.1 [2.0]	2.2 ± 1.9 [1.0]	18.3†	2.2 ± 2.6 [2.0]	2.2 ± 1.7 [1.0]	1.3
No. of outpatient visits per patient, mean ± SD [median]	55.7 ± 42.2 [45.0]	44.9 ± 42.2 [32.0]	25.6†	52.2 ± 57.9 [42.0]	47.6 ± 35.9 [34.0]	9.6
Total overall costs, mean ± SD [median][h]	$65,556 ± 63,220 [47,245]	$50,830 ± 63,882 [29,919]	23.2†	$59,902 ± 81,048 [45,201]	$54,322 ± 55,429 [31,703]	8.0

(continued)

Table 1 (continued). Baseline Characteristics of the Study Population

	Unadjusted			IPTW-Adjusted		
	PP Patients (n = 2,285)	OAA Patients (n = 8,005)	Standardized Difference (%)[a]	PP Patients (n = 5,052)	OAA Patients (n = 5,238)	Standardized Difference (%)[a]
Type of schizophrenia disorder (*ICD-9* code),[i] n (%)						
Schizophreniform disorder (295.4)	41 (1.8)	117 (1.5)	2.6	74 (1.5)	81 (1.5)	0.6
Schizoaffective disorder (295.7)	1,460 (63.9)	4,694 (58.6)	10.8†	3,025 (59.9)	3,129 (59.7)	0.3
Schizophrenia, other (295.0–295.3, 295.5–295.6, 295.8–295.9)	1,855 (81.2)	5,706 (71.3)	23.4†	3,809 (75.4)	3,849 (73.5)	4.4
Physical comorbidities,[j] n (%)						
Psychoses	2,285 (100.0)	8,005 (100.0)	0.0	5,052 (100.0)	5,238 (100.0)	0.0
Depression	1,262 (55.2)	4,991 (62.3)	14.5†	2,792 (55.3)	3,163 (60.4)	10.4†
Hypertension, uncomplicated	1,202 (52.6)	4,575 (57.2)	9.2	3,072 (60.8)	2,962 (56.5)	8.6
Drug abuse	1,138 (49.8)	4,041 (50.5)	1.4	2,418 (47.9)	2,631 (50.2)	4.7
Alcohol abuse	1,096 (48.0)	3,844 (48.0)	0.1	2,391 (47.3)	2,511 (47.9)	1.3
Diabetes without chronic complications	548 (24.0)	2,162 (27.0)	7.0	1,501 (29.7)	1,392 (26.6)	6.9
Chronic pulmonary disease	500 (21.9)	1,989 (24.8)	7.0	1,240 (24.5)	1,278 (24.4)	0.3
Obesity	602 (26.3)	1,868 (23.3)	7.0	1,377 (27.3)	1,257 (24.0)	7.5
Fluid and electrolyte disorders	362 (15.8)	1,324 (16.5)	1.9	816 (16.2)	885 (16.9)	2.0
Liver disease	247 (10.8)	1,007 (12.6)	5.5	628 (12.4)	640 (12.2)	0.6
Other neurologic disorder	227 (9.9)	992 (12.4)	7.8	666 (13.2)	622 (11.9)	4.0
Hypothyroidism	250 (10.9)	789 (9.9)	3.6	562 (11.1)	534 (10.2)	3.0
Mental comorbidities,[k] n (%)						
Other conditions that may require a focus of clinical attention[l]	2,213 (96.8)	7,331 (91.6)	22.7†	4,633 (91.7)	4,857 (92.7)	3.9
Schizophrenia spectrum and other psychotic disorders	2,063 (90.3)	6,786 (84.8)	16.7†	4,359 (86.3)	4,501 (85.9)	1.0
Substance-related and addictive disorders	1,724 (75.4)	5,696 (71.2)	9.7	3,643 (72.1)	3,778 (72.1)	0.1
Depressive disorders	973 (42.6)	4,027 (50.3)	15.5†	2,209 (43.7)	2,529 (48.3)	9.2
Bipolar and related disorders	816 (35.7)	2,621 (32.7)	6.3	1,660 (32.9)	1,748 (33.4)	1.1
Trauma- and stressor-related disorders	655 (28.7)	2,641 (33.0)	9.4	1,496 (29.6)	1,667 (31.8)	4.8
Anxiety disorders	458 (20.0)	1,734 (21.7)	4.0	1,019 (20.2)	1,110 (21.2)	2.5
Sleep-wake disorders	403 (17.6)	1,516 (18.9)	3.4	884 (17.5)	976 (18.6)	3.0
Personality disorders	331 (14.5)	1,410 (17.6)	8.5	765 (15.1)	879 (16.8)	4.5
Other mental disorders	291 (12.7)	1,251 (15.6)	8.3	678 (13.4)	785 (15.0)	4.5
Patient symptom assessment scores						
GAF score, mean ± SD [median]	34.0 ± 14.8 [35.0]	36.8 ± 13.9 [35.0]	19.4†	36.4 ± 20.4 [35.0]	36.2 ± 11.4 [35.0]	0.9

[a]A standardized difference greater than 10% (indicated by dagger symbols) has previously been used to denote a residual imbalance in the matched sample (see Austin[23]).
[b]The length of the study period for each patient is measured from the index date to the earliest of either death or October 31, 2014.
[c]Homelessness identified based on a *ICD-9-CM* diagnosis for V60.0 ("lack of housing") during the baseline period.
[d]Income is measured using the most recent recorded income value prior to the index date (which may occur prior to the baseline period). All income values were inflated to US $2014 values using the All Items component of the Consumer Product Index. Mean income is among patients with known income during the baseline period.
[e]The list of concomitant medications for mental disorder and the corresponding generic product identifier codes are presented in Supplementary eTable 2.
[f]AP polypharmacy was defined as having ≥ 60 consecutive days with overlapping coverage of ≥ 2 unique AP agents. For noninjectable drugs received in the inpatient setting, a 1-day coverage was imputed.
[g]Psychiatric polypharmacy was defined as having ≥ 60 consecutive days with overlapping coverage of ≥ 1 AP agent and ≥ 1 anxiolytic, antidepressant, or mood stabilizer. For noninjectable drugs received in the inpatient setting, a 1-day coverage was imputed.
[h]Cost values were inflated to US $2014 using the Medical Services component of the Consumer Product Index. Total overall costs include inpatient, outpatient, and pharmacy costs.
[i]Types of schizophrenia disorder were identified based on the first 4 digits of the *ICD-9-CM* codes for schizophrenia diagnosis. Note that types of schizophrenia disorder are not mutually exclusive.
[j]Elixhauser et al.[26]
[k]*DSM-5*.[1]
[l]These conditions refer to other conditions and problems that may be a focus of clinical attention or that may otherwise affect the diagnosis, course, prognosis, or treatment of a patient's mental disorder. These conditions include relation problems, abuse and neglect, educational and occupational problems, housing and economic problems, other problems related to the social environment, other health service encounters for counseling and medical advice, and other circumstances of personal history.
Abbreviations: AP = antipsychotic, GAF = Global Assessment of Functioning, IPTW = inverse probability of treatment weight, LAT = long-acting injectable therapy, OAA = oral atypical antipsychotics, PDC = proportion of days covered, PP = paliperidone palmitate, SD = standard deviation.

(IRR = 0.82, $P < .001$) compared to treatment with OAAs. PP was also associated with a 3% increase in the incidence rate of outpatient visits per patient (IRR = 1.03, $P < .001$). This was driven primarily by the fact that PP patients had more frequent MHICM visits (IRR = 1.81, $P < .001$).

Among patients with a mental health inpatient stay, PP patients were less likely to be rehospitalized within 30 days of discharge compared to OAA patients (26.6% vs 29.1%, $P = .010$). HRU following a mental health inpatient visit is presented in Supplementary eTable 1.

Association Between Treatment and Health Care Costs

Adjusted, annualized mean health care costs evaluated during the 12-month study period and adjusted mean cost differences between treatment cohorts are presented in

Table 2. Treatment Patterns Evaluated During the 12-Month Study Period

	PP Patients (n = 5,052)	OAA Patients (n = 5,238)	*P* Value[a]
Index drug treatment patterns			
Duration of treatment,[b] mean ± SD [median]	209.6 ± 182.5 [180.0]	165.0 ± 91.9 [111.0]	<.001*
Patients with ≥ 30-day treatment gap,[c] n (%)	3,599 (71.2)	4,348 (83.0)	<.001*
Patients with ≥ 60-day treatment gap,[c] n (%)	3,060 (60.6)	3,874 (74.0)	<.001*
PDC by index drug, n (%)			
PDC < 0.8	3,245 (64.2)	4,018 (76.7)	<.001*
PDC ≥ 0.8	1,808 (35.8)	1,220 (23.3)	<.001*
No. of unique AP agents received, mean ± SD [median]	2.8 ± 2.4 [2.0]	2.5 ± 1.2 [2.0]	<.001*
PDC by any AP agent, n (%)			
PDC < 0.8	2,793 (55.3)	3,026 (57.8)	.011*
PDC ≥ 0.8	2,259 (44.7)	2,212 (42.2)	.011*
AP use other than index drug, n (%)			
Typical oral and short-term injectable APs	1,650 (32.7)	2,211 (42.2)	<.001*
Atypical oral and short-term injectable APs	4,997 (98.9)	5,237 (100.0)	<.001*
Typical LAT	330 (6.5)	585 (11.2)	<.001*
Atypical LAT	405 (8.0)	614 (11.7)	<.001*
Concomitant medication use,[d] n (%)			
Antidepressant	3,321 (65.7)	3,623 (69.2)	<.001*
Anxiolytics	3,447 (68.2)	3,978 (76.0)	<.001*
Mood stabilizer	1,460 (28.9)	1,796 (34.3)	<.001*
None of the above	593 (11.7)	420 (8.0)	<.001*
Polypharmacy			
AP polypharmacy,[e] n (%)	847 (16.8)	880 (16.8)	.941
Length of AP polypharmacy (days), mean ± SD [median]	226.0 ± 129.1 [229.0]	220.7 ± 73.7 [226.0]	.300
Psychiatric polypharmacy,[f] n (%)	2,036 (40.3)	2,503 (47.8)	<.001*
Length of psychiatric polypharmacy (days), mean ± SD [median]	252.9 ± 122.5 [267.0]	256.7 ± 65.2 [272.0]	.212

[a]*P* values were computed using the weighted *t* test for continuous variables and the weighted χ^2 test for categorical variables.
[b]Mean duration of treatment is calculated by using the minimum of the number of days a patient was observed to receive treatment, allowing a maximum gap of 30 days following the date of dispensing plus day supply. Patients who did not discontinue their index therapy during the 12-month study period are included.
[c]A gap in treatment was identified from the date of dispensing plus day supply greater than the specified number of days.
[d]Concomitant medication use was evaluated in the 12 months post-index. The list of concomitant medications for mental disorder and the corresponding generic product identifier codes are presented in Supplementary eTable 2.
[e]AP polypharmacy was defined as having ≥ 60 consecutive days with overlapping coverage of ≥ 2 unique AP agents. For noninjectable drugs received in the inpatient setting, a 1-day coverage was imputed.
[f]Psychiatric polypharmacy was defined as having ≥ 60 consecutive days with overlapping coverage of ≥ 1 AP agent and ≥ 1 anxiolytic, antidepressant, or mood stabilizer. For noninjectable drugs received in the inpatient setting, a 1-day coverage was imputed.
*$P < .05$.
Abbreviations: AP = antipsychotic, CI = confidence interval, OAA = oral atypical antipsychotics, PDC = proportion of days covered, PP = paliperidone palmitate, SD = standard deviation.

Table 4. Compared to treatment with OAAs, treatment with PP was associated with a mean total all-cause health care (medical and pharmacy) cost difference of –$8,511.36 ($P = .012$). Though PP treatment was associated with greater total outpatient visit costs ($2,527.44, $P < .001$) and higher pharmacy costs ($3,416.96, $P < .001$), this was offset by lower total inpatient stay costs (–$14,455.76, $P < .001$) resulting in total overall cost savings associated with PP relative to OAAs.

In addition, patients treated with PP were 20% more likely to experience an increase in income (OR = 1.20, $P = .027$) and 18% less likely to be homeless (OR = 0.82, $P < .001$) during the 12-month study period compared to patients treated with OAAs (Supplementary eFigure 2). With respect to GAF, patients treated with PP were more likely to experience an improvement in GAF score of at least 10 points (OR = 1.15, $P = .055$).

Results From Sensitivity Analysis Stratified by MHICM Participation at Baseline

With respect to HRU, the benefits of PP persisted in patients who participated in MHICM at baseline and those who did not, though the magnitudes of association were greater among patients with MHICM visits compared to patients without MHICM visits at baseline. Patients without MHICM visits at baseline treated with PP had fewer inpatient stays (IRR = 0.94, $P < .001$), mental health stays (IRR = 0.94, $P < .001$), and long-term care stays (IRR = 0.85, $P = .040$) per patient compared to OAA patients. However, PP patients had a greater number of MHICM visits (IRR = 1.52, $P < .001$). Similar results were seen in patients with MHICM visits at baseline.

As shown in Table 4, the difference in mean total (medical and pharmacy) health care costs between PP and OAA patients was not statistically significant (–$5,221.68, $P = .265$) among non-MHICM patients. While significant total health care cost savings associated with PP are not observed among patients who are not enrolled in MHICM during the baseline period, total health care costs were similar between the PP and OAA cohorts, with significant total inpatient stay cost savings (–$9,718.38, $P = .016$) fully offsetting higher total pharmacy costs ($3,772.64, $P < .001$) in PP patients relative to OAA patients. Among patients with MHICM visits at baseline,

Table 3. Adjusted, Annualized Resource Utilization Evaluated During the 12-Month Study Period

All-Cause Resource Utilization	PP Patients (n = 5,052)[a]	OAA Patients (n = 5,238)[a]	Incidence Rate Ratio (95% CI)[b]	*P* Value[c]
Inpatient stays[d]				
No. of patients with a stay, n (%)	4,211 (83.3)	4,669 (89.1)	…	<.001*
Time to first hospital admission (days)[e]	116.2 ± 149.0 [83.0]	90.6 ± 78.9 [50.0]	…	<.001*
No. of stays per patient	2.3 ± 5.4 [2.0]	2.6 ± 3.0 [2.0]	0.89 (0.87 to 0.91)	<.001*
No. of days in inpatient setting	43.7 ± 104.0 [17.0]	53.4 ± 65.2 [22.0]	0.82 (0.81 to 0.82)	<.001*
Mental health stays				
No. of stays per patient	1.8 ± 4.2 [1.0]	2.0 ± 2.1 [1.0]	0.92 (0.89 to 0.94)	<.001*
No. of days in mental health setting	35.9 ± 90.3 [14.0]	40.6 ± 51.9 [16.0]	0.88 (0.88 to 0.89)	<.001*
Long-term care stays				
No. of stays per patient	0.1 ± 1.5 [0.0]	0.1 ± 0.8 [0.0]	0.62 (0.55 to 0.71)	<.001*
No. of days in long-term care setting	4.5 ± 41.4 [0.0]	7.5 ± 34.0 [0.0]	0.59 (0.58 to 0.60)	<.001*
Other inpatient stays				
No. of stays per patient	0.5 ± 2.0 [0.0]	0.5 ± 1.6 [0.0]	0.84 (0.79 to 0.89)	<.001*
No. of days in other inpatient setting	3.3 ± 17.1 [0.0]	5.3 ± 18.0 [0.0]	0.63 (0.62 to 0.65)	<.001*
Outpatient services				
No. of patients with a visit, n (%)	5,051 (100.0)	5,232 (99.9)	…	.125
No. of visits per patient	69.1 ± 68.4 [59.0]	67.4 ± 41.1 [54.0]	1.03 (1.02 to 1.03)	<.001*
Emergency room visits				
No. of visits per patient	2.3 ± 6.1 [1.0]	2.4 ± 3.5 [1.0]	0.98 (0.95 to 1.00)	.062
Mental health intensive case management visits				
No. of visits per patient	17.9 ± 46.0 [0.0]	9.9 ± 20.3 [0.0]	1.81 (1.79 to 1.82)	<.001*
Other outpatient visits				
No. of visits per patient	48.9 ± 58.8 [37.0]	55.1 ± 36.8 [42.4]	0.89 (0.88 to 0.89)	<.001*

[a]Values expressed as mean ± SD [median] unless otherwise noted.
[b]Incidence rate ratios were estimated from a weighted Poisson regression, using normalized unstabilized IPTW, across the 2 cohorts (for continuous/count variables only).
[c]*P* values were computed using the Wald χ^2 *P* value of the "cohort" variable (from the Poisson regression) for continuous variables and the weighted χ^2 test for categorical variables.
[d]A small proportion (~2%) of patients had concurrent inpatient stays in the VA data. In these cases, both stays are included in the calculation of length of stay.
[e]Time to first hospital admission is among patients with a hospital admission during the 12-month study period. *P* value was computed using a weighted *t* test.
*$P < .05$.
Abbreviations: CI = confidence interval, OAA = oral atypical antipsychotics, PP = paliperidone palmitate, SD = standard deviation. Symbol: … = not applicable.

however, PP patients had significantly lower total all-cause health care costs (–$22,584.16, $P < .001$) compared to OAA patients. Thus, lower total health care costs associated with PP are apparent in patients with MHICM visits at baseline, but the evidence for total health care cost savings is not as definitive for patients who are not enrolled in MHICM during the baseline period.

DISCUSSION

This study found that PP was associated with less frequent all-cause inpatient hospitalizations, more frequent MHICM visits, and improved socioeconomic status during the annualized 12-month follow-up period compared to OAAs. While mean annual pharmacy and outpatient costs were higher among PP users, mean annual inpatient costs were lower, resulting in significant mean annual total cost savings associated with PP relative to OAAs. This is the largest study to examine health care costs and HRU associated with PP use among veterans to date. Given the difficulty of designing generalizable randomized trials of LATs in which improved adherence and persistence is the hypothesized mechanism of incremental benefit relative to oral antipsychotics, observational data are useful to demonstrate the benefit associated with PP and for informing clinical practice.

While PS matching is often used in studies to adjust for differences in baseline confounders, it may result in smaller sample size when appropriate matches between treated and control patients are not found, thus decreasing power. Furthermore, incomplete matching may make it difficult to describe the population of patients for whom matched results apply. The IPTW method applied in this study allows for the preservation of the total sample size while adjusting for baseline confounding, making the results more generalizable to the total population. While some residual confounding may remain after weighting by IPTW, this would result in more conservative estimates of association as the PP cohort has a higher proportion of patients with polypharmacy and a greater number of unique AP agents received at baseline (after weighting), suggesting that severity of disease is slightly greater for the PP cohort than the OAA cohort.

Results from this study are consistent with previous research.[27–30] For instance, Xiao et al[27] found that PP patients had lower medical costs attributable to reduced inpatient and long-term care admissions compared to OAA patients. These lower medical costs offset the higher pharmacy expense for PP-treated patients, resulting in comparable total overall costs and suggesting enhanced clinical management of schizophrenia. Similarly, Baser et al[28] found that PP treatment was associated with lower mean

Table 4. Adjusted, Annualized Health Care Costs Evaluated During the 12-Month Study Period

All-Cause Health Care Costs[a] (US $2014)	PP Patients[b]	OAA Patients[b]	PP vs OAA Cost Difference (95% CI)[c]	*P* Value[c]
Total sample	n = 5,052	n = 5,238		
Total overall costs	$80,604 ± 123,390 [55,359]	$85,740 ± 95,506 [53,646]	−$8,511.36 (−$14,999.07 to −$2,052.16)	.012*
Total medical costs (inpatient + outpatient)	$70,080 ± 116,318 [45,144]	$78,854 ± 87,804 [47,627]	−$11,928.32 (−$17,723.26 to −$5,854.95)	< .001*
Inpatient stay costs				
Total stay costs	$50,390 ± 114,642 [23,228]	$62,004 ± 87,309 [28,816]	-$14,455.76 (−$20,174.09 to −$8,668.08)	< .001*
Mental health costs	$40,339 ± 96,398 [17,327]	$45,889 ± 59,477 [21,128]	−$7,414.95 (−$11,518.39 to −$3,111.15)	< .001*
Long-term care costs	$3,512 ± 36,778 [0]	$5,237 ± 26,563 [0]	−$2,228.12 (−$4,382.38 to $233.45)	.076
Other inpatient costs	$6,539 ± 36,118 [0]	$10,877 ± 56,597 [0]	−$4,812.69 (−$7,356.03 to −$2,224.87)	< .001*
Outpatient visit costs				
Total visit costs	$19,691 ± 25,496 [14,690]	$16,850 ± 13,781 [11,808]	$2,527.44 ($1,346.05 to $3,847.83)	< .001*
Emergency room costs	$2,402 ± 6,447 [896]	$2,403 ± 4,133 [798]	−$59.26 (−$325.95 to $244.57)	.725
MHICM costs	$6,905 ± 19,185 [0]	$3,612 ± 8,166 [0]	$3,114.10 ($2,250.87 to $3,961.39)	< .001*
Other outpatient costs	$10,384 ± 16,044 [6,814]	$10,835 ± 10,035 [7,062]	−$527.41 (−$1,350.81 to $474.45)	.216
Pharmacy costs				
Total pharmacy costs	$10,524 ± 15,799 [7,801]	$6,886 ± 14,982 [4,256]	$3,416.96 ($2,617.48 to $4,188.67)	< .001*
Inpatient pharmacy costs	$3,940 ± 12,155 [1,505]	$3,650 ± 14,430 [1,299]	$117.39 (−$573.49 to $718.48)	.637
Outpatient pharmacy costs	$6,584 ± 10,916 [3,686]	$3,236 ± 4,101 [1,972]	$3,299.58 ($2,783.79 to $3,790.81)	< .001*
Patients with ≥ 1 MHICM visit at baseline	n = 1,565	n = 928		
Total overall costs	$93,951 ± 117,503 [68,423]	$121,448 ± 139,200 [78,769]	−$22,584.16 (−$38,228.38 to −$11,590.64)	< .001*
Inpatient stay costs				
Total stay costs	$53,269 ± 112,817 [29,140]	$84,100 ± 121,648 [40,754]	−$26,454.78 (−$40,795.91 to −$16,766.61)	< .001*
Mental health costs	$43,153 ± 105,459 [15,715]	$62,338 ± 76,666 [28,679]	−$16,014.30 (−$23,228.96 to −$4,512.90)	.004*
Long-term care costs	$1,514 ± 15,474 [0]	$7,776 ± 32,792 [0]	−$5,717.15 (−$8,815.77 to −$3,965.67)	< .001*
Other inpatient costs	$8,602 ± 38,662 [0]	$13,986 ± 89,878 [0]	−$4,723.33 (−$16,766.39 to −$976.30)	.008*
Outpatient visit costs				
Total visit costs	$29,027 ± 28,895 [26,290]	$26,980 ± 17,844 [23,712]	$2,250.17 ($626.55 to $4,891.14)	< .001*
Emergency room costs	$2,492 ± 6,176 [881]	$2,692 ± 4,143 [991]	−$105.51 (−$509.48 to $323.73)	.613
MHICM costs	$18,108 ± 23,200 [17,989]	$14,890 ± 14,456 [12,040]	$3,275.96 ($2,304.97 to $5,588.07)	< .001*
Other outpatient costs	$8,426 ± 15,457 [4,757]	$9,398 ± 9,560 [5,826]	−$920.29 (−$2,244.01 to $174.94)	.116
Pharmacy costs				
Total pharmacy costs	$11,656 ± 14,880 [9,121]	$10,368 ± 32,918 [6,748]	$1,620.46 (−$1,284.82 to $3,039.43)	.293
Inpatient pharmacy costs	$3,689 ± 10,968 [1,330]	$5,798 ± 32,758 [1,974]	−$1,795.38 (−$4,651.89 to −$365.43)	.012*
Outpatient pharmacy costs	$7,966 ± 11,623 [5,012]	$4,570 ± 4,296 [3,213]	$3,415.84 ($2,368.35 to $4,072.89)	< .001*
Patients without MHICM visit at baseline	n = 3,488	n = 4,310		
Total overall costs	$74,616 ± 125,010 [47,373]	$78,051 ± 83,193 [48,572]	−$5,221.68 (−$13,669.21 to $3,532.06)	.265
Inpatient stay costs				
Total stay costs	$49,098 ± 115,454 [22,145]	$57,246 ± 78,431 [26,958]	−$9,718.38 (−$17,573.83 to −$2,589.33)	.016*
Mental health costs	$39,076 ± 91,912 [18,666]	$42,348 ± 55,129 [20,033]	−$4,242.80 (−$10,241.81 to −$743.74)	.024*
Long-term care costs	$4,408 ± 43,109 [0]	$4,690 ± 25,159 [0]	-$617.10 (−$3,751.21 to $3,962.98)	.758
Other inpatient costs	$5,614 ± 34,813 [0]	$10,208 ± 47,513 [0]	-$4,858.48 (−$7,064.04 to −$1,568.27)	< .001*
Outpatient visit costs				
Total visit costs	$15,502 ± 20,962 [11,066]	$14,669 ± 12,157 [9,986]	$724.05 (−$196.10 to $3,743.86)	.096
Emergency room costs	$2,361 ± 6,568 [909]	$2,341 ± 4,129 [755]	−$12.02 (−$304.33 to $791.18)	.601
MHICM costs	$1,878 ± 10,413 [0]	$1,183 ± 4,209 [0]	$694.25 ($129.20 to $1,475.90)	.012*
Other outpatient costs	$11,263 ± 16,140 [7,426]	$11,145 ± 10,108 [7,336]	$41.82 (−$780.79 to $2,471.31)	.441
Pharmacy costs				
Total pharmacy costs	$10,016 ± 16,151 [7,053]	$6,136 ± 7,482 [3,856]	$3,772.64 ($2,780.81 to $5,072.76)	< .001*
Inpatient pharmacy costs	$4,052 ± 12,663 [1,621]	$3,187 ± 6,318 [1,195]	$777.65 ($64.92 to $1,663.98)	.028*
Outpatient pharmacy costs	$5,964 ± 10,448 [3,393]	$2,949 ± 4,026 [1,784]	$2,994.99 ($2,350.78 to $3,735.67)	< .001*

[a]All cost values were inflated to US $2014 using the Medical Services component of the Consumer Product Index.
[b]Values expressed as mean ± SD [median] unless otherwise noted. IPTW-weighted means are presented.
[c]*P* values and confidence intervals (CIs) were computed using bootstrapping with 499 iterations. The outcomes were modeled using normalized, unstabilized IPTW-weighted linear regression with total baseline cost included as a covariate.
*$P < .05$.
Abbreviations: CI = confidence interval, MHICM = mental health intensive case management, OAA = oral atypical antipsychotics, PP = paliperidone palmitate, SD = standard deviation.

inpatient costs, lower hospitalization rates, and a shorter length of stay in inpatient days versus OAA treatment.

In our study, patients treated with PP had higher persistence and lower proportions of patients with 30 or 60 day gaps in treatment than patients treated with OAAs. This may explain the differences observed since improved medication coverage is especially important for schizophrenia patients who are more likely to experience relapse or rehospitalization when they discontinue therapy. LATs like PP provide longer and more persistent medication coverage, and allow clinicians to confirm adherence as the medication is administered via injection by a health care provider. For this reason, it was expected that PP treatment might be associated with greater frequency of outpatient visits and higher outpatient costs compared to treatment with OAAs. The increased frequency of outpatient visits, and especially MHICM visits, also indicates that PP patients may be more engaged in their health and experience greater continuity of care. This is a positive outcome among schizophrenia patients, who often fail to

follow-up with health care providers and skip health care visits.

While the incremental increase is small, the greater proportion of patients experiencing an increase in income and the lower proportion of patients experiencing homelessness during the 12 months following initiation of treatment with PP is promising. Treating schizophrenia patients with PP may give them better opportunities for future employment and positively affect patients' socioeconomic status, which is important as patients with schizophrenia often find themselves in more difficult economic circumstances than the general population.

The general conclusions of the study held in the sensitivity analysis examining subgroups of patients stratified by MHICM participation status at baseline. Statistically significant savings in total health care costs associated with PP were observed only in patients with MHICM visits at baseline, though statistically significant reductions in total inpatient stay costs associated with PP were also observed for patients who were not enrolled in MHICM at baseline. Thus, MHICM participation may be modifying the effect of or interacting with PP (compared to OAA) and contributing to the lower health care costs observed, especially since previous research has demonstrated that MHICM is a cost effective treatment among veterans.[31] In addition, post-baseline MHICM participation may have also impacted the results of this study as a greater number of MHICM visits were observed among PP patients in the post-baseline period for both baseline MHICM stratified groups (ie, patients participating in MHICM visits at baseline and patients not participating in MHICM visits at baseline). While a time-varying analysis of post-index MHICM participation was not part of the current study, this is an important topic that merits exploration in future research.

Limitations

This study has several limitations. For instance, all patients were required to have a GAF score recorded during baseline, which reduced our sample size. Furthermore, the majority of GAF scores captured were assessed during inpatient hospital stays, making the GAF score inclusion requirement essentially a proxy for inpatient hospitalization. Though this was unexpected when inclusion criteria were developed, imposing this criterion may have helped ensure similar acuity of illness and disease severity in OAA and PP patients. Patients with more severe disease are more likely to be hospitalized with schizophrenia and would be in greater need of interventions to improve symptoms. In addition, including this criterion was important to ensure all patients had a baseline functioning score that could be adjusted for by including the variable in the model used to construct IPTW. Thus, while the GAF score requirement may be a limitation, it also may have strengthened the analysis.

Also, almost all patients in the PP cohort used atypical oral and short-term injectable antipsychotics during the follow-up period. This may be due to the fact that OAAs are used to treat a number of mental health comorbidities that co-occur with schizophrenia, such as depression and bipolar disorder as well as insomnia, or it may be that these agents are adjunctive support for management of schizophrenia symptoms. In addition, this study does not consider whether patients switch treatment during the observation period. Rather, the analysis took an "intention-to-treat" approach that likely resulted in conservative estimates of association as many patients in the OAA cohort had LAT dispensings during the study period. Sixty percent of PP users and 74% of AP users had a treatment gap of at least 60 days, indicating that there may be partial or full overlap of medications when patients are being switched to a new antipsychotic, as evidenced by the 17% of PP and OAA patients with antipsychotic polypharmacy.

Findings from this study may be limited in their generalizability to the total US population as the study sample was specific to veterans obtaining health care through the VHA system, who may have very different characteristics and comorbidities compared to the general population. Specifically, less than 10% of our study sample consisted of women. Also, as with all retrospective observational studies, the results may be subject to selection bias and residual confounding by unmeasured confounders, though a large number of covariates were included when building the IPTW. While outcomes such as relapse and adverse events associated with PP or OAA treatment may be of interest and warranted in a future study, they were not assessed in the current study.

CONCLUSIONS

With its once monthly injection, PP was associated with improvements in adherence, reduced hospitalization rates, and improved socioeconomic standing among veterans with schizophrenia. Although more frequent MHICM visits among PP patients during the observation period may have contributed to differences observed relative to OAA patients, the greater pharmacy cost observed among PP patients was more than offset by reductions in inpatient costs resulting in average annual total health care (medical and pharmacy) cost savings of more than $8,000 per patient. Thus, PP appears to be a promising treatment option for schizophrenia with the potential to reduce hospitalizations as well as health care costs compared to OAA therapy.

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Drug names: aripiprazole (Abilify and others), asenapine (Saphris), iloperidone (Fanapt), lurasidone (Latuda), olanzapine (Zyprexa and others), paliperidone oral (Invega and others), paliperidone palmitate (Invega Sustenna), quetiapine (Seroquel and others), risperidone (Risperdal and others), ziprasidone (Geodon and others).

Potential conflicts of interest: **Drs Muser** and **Fu** are employees of Janssen Scientific Affairs, LLC. **Drs Duh** and **DerSarkissian**, **Mss Faust** and **Bhak**, and **Messrs Kageleiry** and **Lefebvre** are employees of Analysis Group, Inc which receives research grants from Janssen Scientific Affairs, LLC. **Drs Young-Xu** and **Shiner** declare no conflicts of interest.

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Supplementary material follows this article.

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Supplementary Material

Article Title: Impact of Paliperidone Palmitate Versus Oral Atypical Antipsychotics on Health Care Resource Use and Costs in Veterans With Schizophrenia

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List of Supplementary Material for the article

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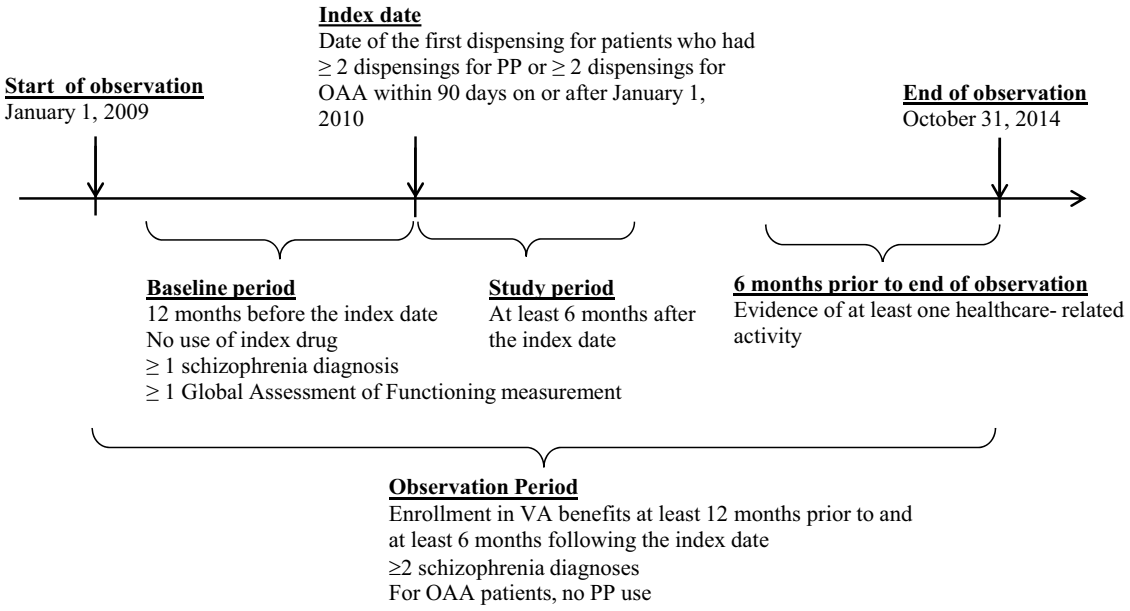
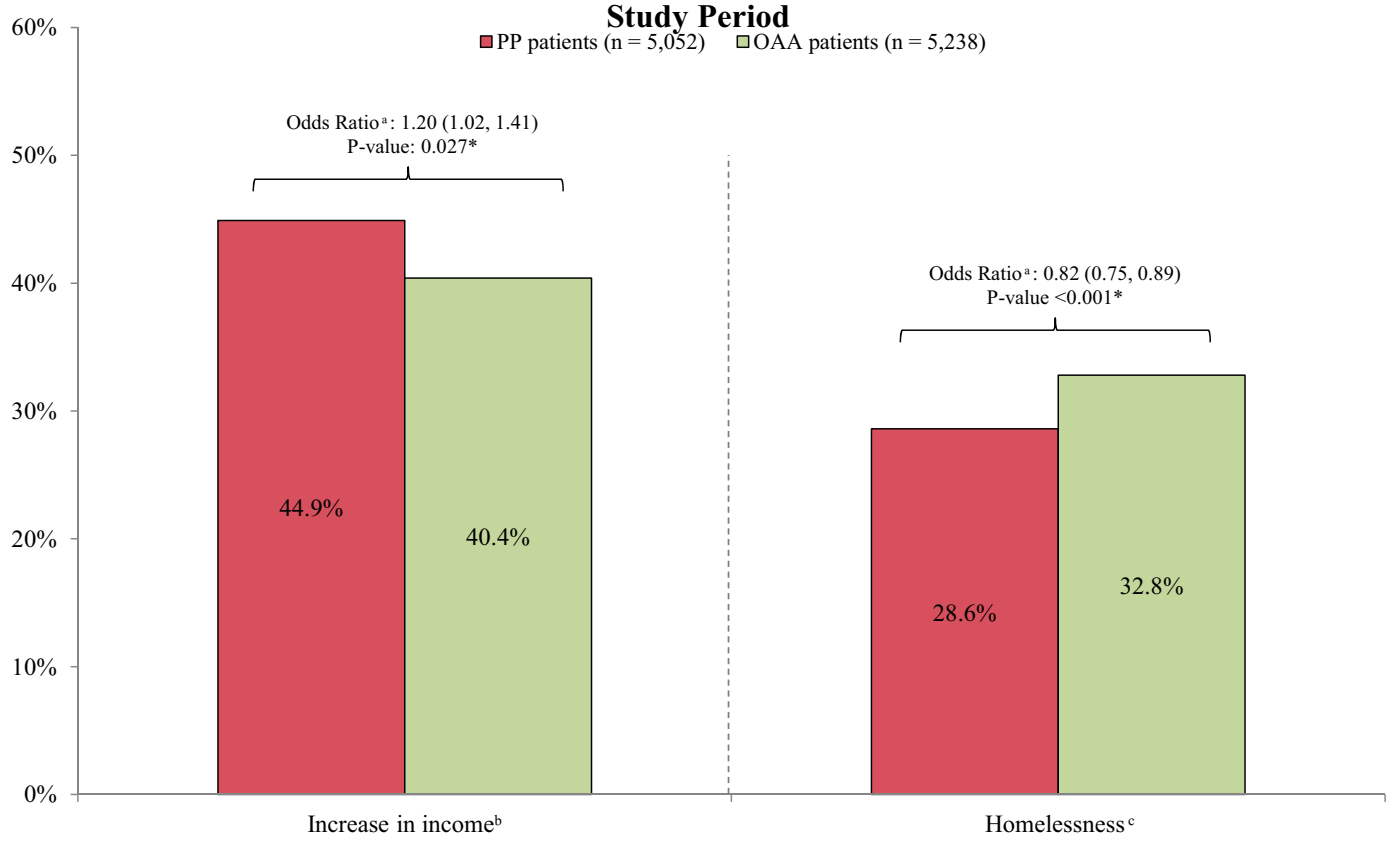
Supplementary eFigure 1. Study Schematic



Supplementary eFigure 2. Adjusted Economic Outcomes During the 12-Month Study Period



Notes:

a. Odds ratios and p-values were estimated from a weighted logistic regression across the two cohorts.

b. Income is reported for the patients with means tests observations during the study period (21.8% of PP patients and 24.3% of OAA patients). Income during the study period is measured using the highest recorded income value. All values were inflated to $2014 using the All Items component of the Consumer Product Index (CPI).

c. Homelessness identified based on a ICD-9-CM diagnosis for V60.0 ("lack of housing") during the study period.

Supplementary eTable 1. Adjusted, Annualized Resource Utilization Evaluated During the 12-Month Study Period Following a Mental Health Inpatient Visit

All-cause resource utilization	All PP patients (n = 5,052)	All OAA patients (n = 5,238)	P value[a]
Number of patients with a mental health inpatient stay, n (%)	4,039 (79.9%)	4,338 (82.8%)	<0.001 *
Inpatient stay within 7 days of discharge[b]	476 (11.8%)	627 (14.5%)	<0.001 *
Mental health stay	430 (10.6%)	559 (12.9%)	0.001 *
Long-term care stay	5 (0.1%)	10 (0.2%)	0.209
Other inpatient stay	68 (1.7%)	102 (2.4%)	0.031 *
Outpatient service within 7 days of discharge[b]	3,770 (93.3%)	3,925 (90.5%)	<0.001 *
Emergency room visit	494 (12.2%)	677 (15.6%)	<0.001 *
Mental health intensive case management visit	1,082 (26.8%)	720 (16.6%)	<0.001 *
Other outpatient visits	3,517 (87.1%)	3,778 (87.1%)	0.987
Inpatient stay within 30 days of discharge[b]	1,074 (26.6%)	1,263 (29.1%)	0.010 *
Mental health stay	937 (23.2%)	1,114 (25.7%)	0.009 *
Long-term care stay	10 (0.3%)	40 (0.9%)	<0.001 *
Other inpatient stay	241 (6.0%)	290 (6.7%)	0.175
Outpatient service within 30 days of discharge[b]	3,951 (97.8%)	4,167 (96.1%)	<0.001 *
Emergency room visit	1,234 (30.5%)	1,283 (29.6%)	0.332
Mental health intensive case management visit	1,242 (30.8%)	870 (20.0%)	<0.001 *
Other outpatient visits	3,816 (94.5%)	4,097 (94.5%)	0.972

* P value < 0.05.

Notes:

a. P values were computed using the weighted chi-square test for categorical variables.

b. Percentages are among those with a mental health inpatient stay during the 12-month study period.

Abbreviations: OAA = oral atypical antipsychotic; PP = paliperidone palmitate.

Supplementary eTable 2. GPI codes for concomitant medication for mental disorder

Category	Name	GPI
Antidepressant	MIRTAZAPINE	58 03 00 50 00
	ISOCARBOXAZID	58 10 00 10 00
	MOCLOBEMIDE	58 10 00 15 00
	PHENELZINE SULFATE	58 10 00 20 10
	SELEGILINE	58 10 00 27 00
	TRANYLCYPROMINE SULFATE	58 10 00 30 10
	NEFAZODONE HCL	58 12 00 50 10
	REBOXETINE MESYLATE	58 12 00 65 10
	TRAZODONE HCL	58 12 00 80 10
	VILAZODONE HCL	58 12 00 88 10
	VORTIOXETINE HBR	58 12 00 93 10
	CITALOPRAM HYDROBROMIDE	58 16 00 20 10
	ESCITALOPRAM	58 16 00 34 00
	ESCITALOPRAM OXALATE	58 16 00 34 10
	FLUOXETINE HCL	58 16 00 40 00
	FLUVOXAMINE MALEATE	58 16 00 45 10
	PAROXETINE HCL	58 16 00 60 00
	PAROXETINE MESYLATE	58 16 00 60 30
	SERTRALINE HCL	58 16 00 70 10
	DESVENLAFAXINE	58 18 00 20 00
	DESVENLAFAXINE SUCCINATE	58 18 00 20 20
	DULOXETINE HCL	58 18 00 25 10
	LEVOMILNACIPRAN	58 18 00 50 00
	LEVOMILNACIPRAN HCL	58 18 00 50 10
	EFFEXOR XR	58 18 00 90 10
	AMINEPTINE HCL	58 20 00 07 10
	AMITRIPTYLINE EMBONATE	58 20 00 10 05
	AMITRIPTYLINE HCL	58 20 00 10 10
	AMOXAPINE	58 20 00 20 00
	BUTRIPTYLINE HCL	58 20 00 23 10
	CLOMIPRAMINE HCL	58 20 00 25 10
	DESIPRAMINE DIBUDINATE	58 20 00 30 05
	DESIPRAMINE HCL	58 20 00 30 10
	DIBENZEPIN HCL	58 20 00 32 10
	DOTHIEPIN HCL	58 20 00 35 10
	DOXEPIN HCL	58 20 00 40 10
	IMIPRAMINE HCL	58 20 00 50 10
	IMIPRAMINE PAMOATE	58 20 00 50 20
	LOFEPRAMINE HCL	58 20 00 53 10
	MIANSERIN HCL	58 20 00 56 10
	NORTRIPTYLINE HCL	58 20 00 60 10
	PROTRIPTYLINE HCL	58 20 00 70 10
	TIANEPTINE SODIUM	58 20 00 76 10
	TRIMIPRAMINE	58 20 00 80 00
	TRIMIPRAMINE MALEATE	58 20 00 80 10
	RESERVE 3	58 30 00 02 00
	AGOMELATINE	58 30 00 04 00
	MAPROTILINE HCL	58 30 00 10 10
	NOMIFENSINE MALEATE	58 30 00 20 10
	BUPROPION HCL	58 30 00 40 10
	BUPROPION HYDROBROMIDE	58 30 00 40 20
	VILOXAZINE HCL	58 30 00 90 10
	TRAZODONE HCL-DIETARY MANAGEMENT PRODUCT	58 99 80 02 75
	CITALOPRAM & DIETARY MANAGEMENT PRODUCT	58 99 85 02 20
	FLUOXETINE HCL-DIETARY MANAGEMENT PRODUCT	58 99 85 02 45
	AMITRIPTYLINE HCL & DIETARY MANAGEMENT PRODUCT	58 99 87 02 10
	BUPROPION HCL-DIETARY MANAGEMENT PRODUCT	58 99 90 02 20
	DOXEPIN HCL (SLEEP)	60 40 00 30 10
	BUPROPION HCL	62 10 00 02 10
	FLUOXETINE HCL (PMDD)	62 20 60 40 00
	PAROXETINE MESYLATE (VASOMOTOR)	62 22 60 60 30
	PERPHENAZINE W/ AMITRIPTYLINE-DIAZEPAM	62 99 00 03 20
	CHLORDIAZEPOXIDE-AMITRIPTYLINE	62 99 20 02 20
	PERPHENAZINE-AMITRIPTYLINE	62 99 40 02 60
	PERPHENAZINE-NORTRIPTYLINE	62 99 40 02 65
	OLANZAPINE-FLUOXETINE HCL	62 99 50 02 50

Supplementary eTable 2. GPI codes for concomitant medication for mental disorder

Category	Name	GPI
Anxiolytics	ALPRAZOLAM	57 10 00 10 00
	BROMAZEPAM	57 10 00 15 00
	CHLORDIAZEPOXIDE	57 10 00 20 00
	CHLORDIAZEPOXIDE HCL	57 10 00 20 10
	CLOBAZAM (ANTIANXIETY)	57 10 00 25 00
	CLORAZEPATE DIPOTASSIUM	57 10 00 30 10
	CLOXAZOLAM	57 10 00 35 00
	DIAZEPAM	57 10 00 40 00
	ETHYL LOFLAZEPATE	57 10 00 45 10
	HALAZEPAM	57 10 00 50 00
	KETAZOLAM	57 10 00 55 00
	LORAZEPAM	57 10 00 60 00
	OXAZEPAM	57 10 00 70 00
	PRAZEPAM	57 10 00 80 00
	TETRAZEPAM	57 10 00 90 00
	BUSPIRONE HCL	57 20 00 05 10
	CHLORMEZANONE	57 20 00 10 00
	DROPERIDOL	57 20 00 30 00
	ETIFOXINE HCL	57 20 00 33 10
	HYDROXYZINE HCL	57 20 00 40 10
	HYDROXYZINE PAMOATE	57 20 00 40 20
	MEPROBAMATE	57 20 00 50 00
	TYBAMATE	57 20 00 60 00
	ALPRAZOLAM INTENSOL	57 99 90 02 10
	DIAZEPAM-DIETARY MANAGEMENT PRODUCT	57 99 90 02 20
	ESTAZOLAM	60 20 10 05 00
	FLUNITRAZEPAM	60 20 10 08 00
	FLURAZEPAM HCL	60 20 10 10 10
	LOPRAZOLAM MESYLATE	60 20 10 17 20
	LORMETAZEPAM	60 20 10 20 00
	MIDAZOLAM	60 20 10 25 00
	MIDAZOLAM HCL	60 20 10 25 10
	MIDAZOLAM HCL-SODIUM CHLORIDE	60 20 10 25 12
	MIDAZOLAM MALEATE	60 20 10 25 20
	NITRAZEPAM	60 20 10 26 00
	QUAZEPAM	60 20 10 28 00
	TEMAZEPAM	60 20 10 30 00
	TRIAZOLAM	60 20 10 40 00
	TEMAZEPAM-DIETARY MANAGEMENT PRODUCT	60 99 80 02 70
	CHLORDIAZEPOXIDE HCL	62 99 20 02 25
	CLONAZEPAM	72 10 00 10 00
	DIAZEPAM (ANTICONVULSANT)	72 10 00 30 00
Mood Stabilizer	LITHIUM	59 50 00 10 10
	LITHIUM CITRATE	59 50 00 10 20
	GABAPENTIN (PHN)	62 54 00 30 00
	GABAPENTIN ENACARBIL	62 56 00 30 20
	DEPAKOTE ER	72 50 00 10 10
	VALPROATE SODIUM	72 50 00 20 10
	VALPROATE MAGNESIUM	72 50 00 20 20
	STAVZOR	72 50 00 30 00
	CARBAMAZEPINE	72 60 00 20 00
	GABAPENTIN	72 60 00 30 00
	LAMICTAL (BLUE)	72 60 00 40 00
	OXCARBAZEPINE	72 60 00 46 00
	TOPIRAMATE	72 60 00 75 00
	GABAPENTIN-DIETARY MANAGEMENT PRODUCT	72 99 60 02 30