ORIGINAL RESEARCH

# Factors Associated with Adherence to the HEDIS Quality Measure in Medicaid Patients with Schizophrenia

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**BACKGROUND:** Treatment continuity is a major challenge in the long-term management of patients with schizophrenia; poor patient adherence to antipsychotic drugs has been associated with negative clinical outcomes. Long-acting injectable therapies may improve adherence and lessen the risk for psychiatric-related relapse, often leading to rehospitalization and higher healthcare costs. Therefore, understanding the determinants of adherence to antipsychotics is critical in the management of patients with schizophrenia.

**OBJECTIVE:** To assess the impact of baseline patient characteristics on adherence as measured by the Healthcare Effectiveness Data and Information Set (HEDIS) measure of continuity of antipsychotic medications among patients with Medicaid coverage.

**METHODS:** Medicaid healthcare claims data between 2008 and 2011 from 5 states were used to identify patients who were diagnosed with schizophrenia (aged 25-64 years) and received ≥1 antipsychotic prescriptions in baseline year 2010 and in measurement year 2011. The HEDIS continuity of antipsychotic medications (ie, adherence) measure was defined as the proportion of days covered with any antipsychotic medication ≥80% during the measurement year. The 2 cohorts compared paliperidone palmitate with any other antipsychotics, including quetiapine, risperidone, and haloperidol. The baseline-year characteristics were evaluated as potential predictive factors of adherence in the measurement year using multivariate logistic regressions. The regression models incorporated the inverse probability of treatment weights to control for differences in baseline characteristics between the paliperidone palmitate and the other antipsychotics cohort.

**RESULTS:** Among the 12,990 patients who received an antipsychotic during the study period, 48.6% successfully achieved the continuity criteria in the measurement year. After controlling for other covariates, the odds of adherence were improved by adherence at baseline (odds ratio [OR], 9.42; 95% confidence interval [CI], 8.55-10.39). The use of paliperidone palmitate was associated with a 26% increase in the odds of achieving adherence compared with the use of the other antipsychotics studied (OR, 1.26; 95% CI, 1.14-1.39). In addition, female sex (OR, 1.11; 95% CI, 1.01-1.22), age 55 to 64 years (OR, 1.26; 95% CI, 1.09-1.46) versus age 25 to 34 years, Hispanic race (OR, 1.37; 95% CI, 1.05-1.81) versus white race, and an increase of $10,000 in baseline inpatient costs (OR, 1.11; 95% CI, 1.08-1.15) were associated with greater odds of treatment continuity.

**CONCLUSIONS:** In addition to sex, age, and race, the baseline characteristics that were associated with achieving the HEDIS continuity of antipsychotic medication measure included previous-year adherence, inpatient costs, and the use of paliperidone palmitate. These findings offer insight to healthcare plans that cover Medicaid populations on the effects that patient characteristics and treatment types may have on adherence among patients with schizophrenia.

**KEY WORDS:** adherence, antipsychotics, HEDIS, Medicaid, NCQA, paliperidone palmitate, persistence, schizophrenia

Stakeholder Perspective, page 410

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## KEY POINTS

- Adherence to medications is an ongoing challenge in patients with schizophrenia.
- The use of long-acting injectable antipsychotics is associated with improved adherence compared with oral antipsychotics in patients with schizophrenia.
- In 2013, the NCQA introduced a new HEDIS measure focused on adherence to antipsychotic medications in patients with schizophrenia who are covered by Medicaid plans.
- This study compared adherence to the HEDIS measure among patients with schizophrenia receiving paliperidone palmitate, the first once-monthly long-acting injectable therapy in the United States, or other antipsychotic medications.
- Previous-year adherence to the new HEDIS measure, inpatient costs, and the use of paliperidone palmitate were predictive of adherence.
- Other drivers for adherence to the HEDIS measure were higher inpatient costs reflecting in-hospital therapy, older age, female sex, and Hispanic ethnicity.

Schizophrenia is a devastating psychiatric disorder with a global median lifetime prevalence of 4 per 1000 and a lifetime morbidity risk of 7.2 per 1000.[1] The treatment of schizophrenia has been focused on eliminating the symptoms of the disease and has included antipsychotic medications since the 1950s.[2,3] Despite the development of new therapies for managing schizophrenia, including second-generation (or atypical) antipsychotics, approximately 66% of individuals with this serious mental illness have persisting or fluctuating symptoms even with optimal treatment.[4,5] Throughout their lifetimes, most patients will experience chronic disease with repeated relapses, characterized by exacerbation of psychosis resulting in emergency department visits and costly rehospitalizations.[6-8]

Poor adherence to antipsychotics, particularly to oral formulations, has been associated with increased risks for disease relapse, hospitalizations, and suicide,[9] and has been shown in various studies to have significant direct and indirect costs.[10,11] With an annual excess direct healthcare cost in the United States estimated at $22.7 billion annually in 2002, nonadherence to medication, which affects approximately 50% of patients with schizophrenia, is a critical clinical issue and a major concern for payers.[12-16]

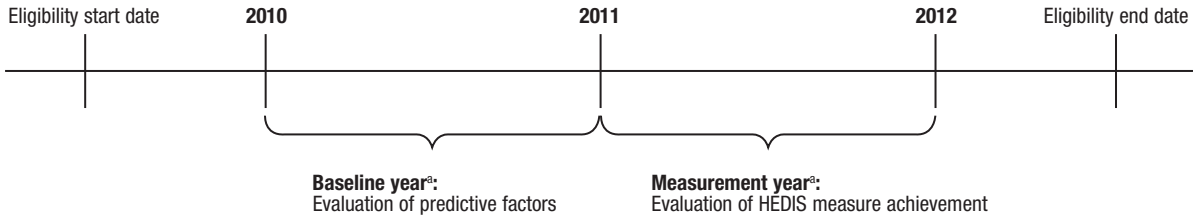
The Healthcare Effectiveness Data and Information Set (HEDIS) measures, which were developed by the National Committee for Quality Assurance (NCQA), are a key tool in evaluating the quality of patient care and are used by more than 90% of healthcare plans and by many leading employers and regulators in the United States.[17] In 2013, a HEDIS quality measure for Medicaid plans was introduced that represented the proportion of a plan's patients with schizophrenia who met a defined threshold of treatment continuity or adherence. On a patient level, treatment continuity was measured as the proportion of days covered (PDC) by antipsychotic medication, calculated from dispensed prescription claims. HEDIS considered a patient to have achieved continuity of treatment if the PDC was ≥80%.[18] Treatment continuity (ie, adherence) is a major challenge in the long-term management of patients with schizophrenia, because poor patient adherence to antipsychotics has been associated with negative clinical outcomes.[19,20]

Understanding the determinants of adherence to antipsychotic medication is critical in the management of patients with schizophrenia. Patient-related factors related to adherence include demographic characteristics (eg, age, socioeconomic status, alcohol or drug use, ethnicity) and general cognitive functions (eg, IQ score, memory, learning abilities).[21,22] The severity of the disease and the perception about illness (eg, the presence of positive or negative perceptions) may also influence patient adherence to antipsychotic medications.[21,22] Medication characteristics, such as side effects and the frequency of administration, can play an important role in adherence to treatment, as well as the complexity of the healthcare system that may limit access to medications, such as a lack of continuity of care. Support from providers, family, and caregivers can tremendously improve the attitude of patients toward their illness and their need for medication, can guide them through the healthcare system, and can provide interventions quickly when patients stop taking their medications.[22]

With less frequent administration than oral formulations, long-acting injectable antipsychotic medications, including paliperidone palmitate, and injectable versions of risperidone and haloperidol, have been associated with lower rates of nonadherence compared with oral equivalents or with patients receiving any oral antipsychotics (eg, oral risperidone, quetiapine, or oral aripiprazole).[23,24] Other potential benefits of long-acting injectable antipsychotics include minimizing disease relapses and lowering hospital admissions, findings that were documented in recent meta-analyses of nonrandomized observational studies.[24-28]

Approved by the US Food and Drug Administration (FDA) in 2009, paliperidone palmitate is the first once-monthly long-acting injectable antipsychotic for the acute and maintenance treatment of schizophrenia in adults.[29]

**Figure 1** Study Design




[a]For Florida, the definitions of the baseline and the measurement years were shifted by 1 quarter, because data for the fourth quarter of 2011 were not available.
HEDIS indicates Healthcare Effectiveness Data and Information Set.

The current study uses important variables such as patient demographic and clinical baseline characteristics, including previous-year adherence and the use of paliperidone palmitate, on the likelihood of achieving the HEDIS antipsychotic continuity measure during the measurement year among patients with schizophrenia using real-world claims data from 5 states offering Medicaid coverage.

## Methods

To control for confounding factors associated with the choice of antipsychotic treatment, inverse probability of treatment weights was used.

The study population was identified using medical and pharmacy claims from Medicaid databases for Florida, New Jersey, Iowa, Missouri, and Kansas for the years 2008 to 2011. Medicaid databases contain medical claims (eg, type of service, service unit, date, *International Classification of Diseases, Ninth Revision* [*ICD-9*] diagnoses, *Current Procedural Terminology* codes, physician specialty, and type of provider), prescription drug claims (eg, supply days, units, date of service, and National Drug Codes), and eligibility information (eg, age, sex, enrollment start and end dates, and date and year of death, if applicable).

### *Study Design*

To approximate the HEDIS metric, this study used a retrospective longitudinal cohort design with calendar year baseline and measurement periods. The baseline (or reference) year, during which patient characteristics were observed to establish a reference, was 2010; the measurement (or index) year, during which the study end points were evaluated, was 2011.

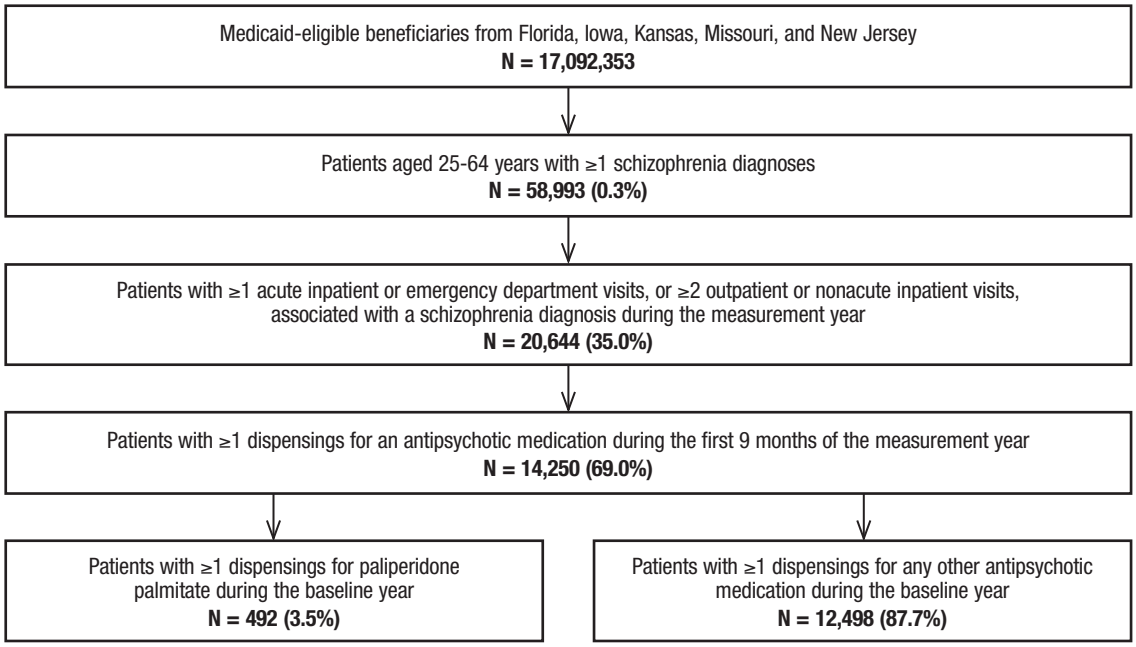
For Florida only, the definitions of the baseline and measurement years were shifted by 1 quarter, because data were not available for the fourth quarter of 2011 at the time this study was conducted. **Figure 1** depicts the design scheme for this study.

The study population was identified according to the specifications set by the NCQA[30,31] and consisted of Medicaid patients (1) with ≥1 acute inpatient or emergency department visits or ≥2 outpatient or nonacute inpatient visits with schizophrenia as the principal diagnosis (*ICD-9* code, 295.xx) during the measurement year 2011; (2) aged 25 to 64 years; (3) with continuous Medicaid enrollment for years 2010 and 2011; (4) with ≥1 dispensed antipsychotic medications (ie, typical or atypical antipsychotic with a general product identifier [GPI] code beginning with 59, and Healthcare Common Procedure Coding System [HCPCS] codes C9125, J1630, J1631, J2794, or S0163) within the first 9 months of the measurement year; and receiving an antipsychotic during the baseline year. Of note, only adults aged >25 years were analyzed in accordance with the HEDIS 2013 measures that were available at the time of the study. The patients were classified into 2 mutually exclusive cohorts, including patients with any paliperidone palmitate claim (GPI code beginning with 590700501018, and HCPCS codes C9255 or J2426) and any other antipsychotic medications users—patients with a claim for an antipsychotic, including quetiapine, risperidone, and haloperidol, but no claim for paliperidone palmitate (see **Appendix, Table 1**, at www.AHDBonline.com for a complete list of medications). Of note, aripiprazole injectable is a once-monthly injectable antipsychotic agent approved by the FDA, but it was not yet available during this study.

Performance on the HEDIS continuity of antipsychotic medications measure was evaluated for the measurement year using the methodology developed by the NCQA, which was defined as achieving a PDC of ≥80% during the measurement year. PDC was defined as the number of nonoverlapping days of supply divided by the number of days in the measurement year (365 days).

For long-acting injectable antipsychotics reimbursed through a medical claim with no days of supply field, the days of supply was imputed from the drug label (eg, 28

**Figure 2** Sample Selection Flow Chart




days of supply were imputed for paliperidone palmitate medical claims). The baseline year and the period up to 2 years before the baseline year were used to identify potential predictive factors from those observable on medical and prescription claims.

### *Study End Points and Statistical Analysis*

The potential predictive factors, which were evaluated during the baseline year, included age, sex, race, state, Quan Charlson Comorbidity Index, healthcare costs, type of antipsychotic treatment prescribed (eg, paliperidone palmitate or other antipsychotic medications, including quetiapine, risperidone, and haloperidol) and adherence status (PDC ≥80%). The healthcare costs and type of antipsychotic treatment received up to 2 years before baseline were also included as predictive factors. The medical and pharmacy costs were evaluated on an annual basis; the medical costs were stratified by place of service (ie, inpatient, outpatient, emergency department, home visit, long-term care, mental institute, and other), and all costs were inflated to 2011 US dollars. *P* values testing the difference between the paliperidone palmitate cohort and the other antipsychotics cohort were calculated using chi-square tests for categorical variables and student's *t*-tests for continuous variables.

As with any real-world study, there is a risk that patients who are prescribed different medications may vary in terms of disease severity or other characteristics. To minimize the potential confounding factors between patients receiving paliperidone palmitate and those receiving other antipsychotics, and in an attempt to keep all patients in the analysis (therefore maximizing the representativeness and generalizability of the results), we used inverse probability of treatment weights based on propensity score.[32-34] The propensity score, which summarizes covariate information about treatment selection into a scalar value, was calculated as the probability of being in the paliperidone palmitate cohort using a multivariate logistic regression based on age, sex, race, state, and past medical healthcare costs. These baseline variables were included as potential confounding factors between the paliperidone palmitate group and the other antipsychotics treatment group.

The weights were calculated as 1/propensity score for the paliperidone palmitate cohort and 1/(1–propensity score) for the other antipsychotics cohort and was normalized using the average weight. For example, a patient receiving paliperidone palmitate with a low predicted probability of receiving this drug (based on the propensity score) received a "high" weight, whereas a paliperidone palmitate user with a high predicted probability received a "low" weight. Weights were truncated at 1% and 99% of the distribution to limit the effect of extreme weights.

Weighted multivariate logistic regression models and odds ratios (ORs) were used to identify potential factors associated with adherence to the HEDIS continuity of antipsychotic measure, including age, sex, race, state,

**Table 1** Patient Baseline Demographics and Clinical Characteristics

| | Paliperidone palmitate users (N = 492) | Other antipsychotics users (N = 12,498) | *P* value[a] |
|---|---|---|---|
| Age at index date, mean ± SD [median] | 42.5 ± 10.5 [43.0] | 46.5 ± 10.5 [48.0] | <.0001 |
| Age range, N (%) | | | |
| 25-34 yrs | 144 (29.3) | 2185 (17.5) | <.0001 |
| 35-44 yrs | 121 (24.6) | 2604 (20.8) | |
| 45-54 yrs | 149 (30.3) | 4475 (35.8) | |
| 55-64 yrs | 78 (15.9) | 3234 (25.9) | |
| Female, N (%) | 211 (42.9) | 5777 (46.2) | .1452 |
| Race, N (%) | | | |
| White | 266 (54.1) | 6560 (52.5) | <.0001 |
| Black | 185 (37.6) | 3808 (30.5) | |
| Hispanic | 3 (0.6) | 879 (7.0) | |
| Other | 35 (7.1) | 1174 (9.4) | |
| Unknown | 3 (0.6) | 77 (0.6) | |
| State, N (%) | | | |
| Florida | 6 (1.2) | 3027 (24.2) | <.0001 |
| Iowa | 5 (1.0) | 366 (2.9) | |
| Kansas | 55 (11.2) | 577 (4.6) | |
| Missouri | 273 (55.5) | 4217 (33.7) | |
| New Jersey | 153 (31.1) | 4311 (34.5) | |
| Quan Charlson Comorbidity Index, mean ± SD [median] | 1.1 ± 1.6 [1.0] | 1.5 ± 2.0 [1.0] | <.0001 |
| PDC, mean ± SD [median] | 0.66 ± 0.26 [0.71] | 0.65 ± 0.28 [0.74] | .6926 |
| PDC ≥80%, N (%) | 197 (40.0) | 5459 (43.7) | .1104 |
| Previous use of antipsychotics | | | |
| 1 year before baseline | 433 (88.0) | 11,046 (88.4) | .7996 |
| 2 years before baseline | 384 (78.0) | 9844 (78.8) | .7035 |
| Healthcare costs, mean ± SD [median], $[b] | | | |
| **Baseline year** | | | |
| Pharmacy costs | | | |
| All pharmacy costs | 9662 ± 10,742 [7852] | 6738 ± 8598 [3651] | <.0001 |
| Antipsychotic medication costs | 7512 ± 7803 [6277] | 3821 ± 5244 [1328] | <.0001 |
| Medical costs | | | |
| Inpatient costs | 9061 ± 20,376 [185] | 4289 ± 15,520 [0] | <.0001 |
| Outpatient costs | 2551 ± 5626 [862] | 6463 ± 16,744 [1342] | <.0001 |
| Emergency department costs | 323 ± 697 [44] | 329 ± 956 [0] | .8543 |
| Home visit costs | 2285 ± 8855 [0] | 2743 ± 10,915 [0] | .2655 |
| Long-term care costs | 1379 ± 6429 [0] | 1562 ± 10,744 [0] | .5505 |
| Mental institute costs | 5522 ± 8454 [1774] | 3179 ± 10,191 [0] | <.0001 |
| Other costs | 1506 ± 5834 [0] | 816 ± 6103 [0] | .0138 |
| Total pharmacy and medical costs | 32,290 ± 32,586 [22,456] | 26,119 ± 32,965 [15,554] | <.0001 |

*Continued*

**Table 1** Patient Baseline Demographics and Clinical Characteristics *(Continued)*

| | Paliperidone palmitate users (N = 492) | Other antipsychotics users (N = 12,498) | *P* value[a] |
|---|---|---|---|
| **1 year before baseline** | | | |
| Medical costs | | | |
| Inpatient costs | 7994 ± 27,902 [0] | 4412 ± 18,311 [0] | .0049 |
| Outpatient costs | 3136 ± 8811 [851] | 6939 ± 21,951 [1312] | <.0001 |
| Emergency department costs | 386 ± 1607 [0] | 370 ± 1617 [0] | .8273 |
| Home visit costs | 1796 ± 5348 [0] | 2335 ± 12,022 [0] | .0415 |
| Long-term care costs | 1225 ± 8217 [0] | 3030 ± 34,939 [0] | .0002 |
| Mental institute costs | 5108 ± 12,881 [353] | 3349 ± 13,921 [0] | .0032 |
| Other costs | 2436 ± 9002 [0] | 1386 ± 10,648 [0] | .0121 |
| **2 years before baseline** | | | |
| Medical costs | | | |
| Inpatient costs | 4264 ± 11,517 [0] | 3517 ± 20,458 [0] | .1758 |
| Outpatient costs | 3437 ± 11,369 [584] | 5024 ± 17,726 [924] | .0032 |
| Emergency department costs | 300 ± 1056 [0] | 295 ± 1309 [0] | .9055 |
| Home visit costs | 1429 ± 4574 [0] | 2042 ± 8572 [0] | .0055 |
| Long-term care costs | 2836 ± 22,951 [0] | 3986 ± 32,747 [0] | .2852 |
| Mental institute costs | 4977 ± 11,664 [67] | 3781 ± 19,477 [0] | .0313 |
| Other costs | 2329 ± 12,850 [0] | 1361 ± 13,127 [0] | .1084 |

[a]Statistical differences between cohorts were calculated using chi-square tests for categorical variables and 2-sided student's *t*-tests for continuous variables.
[b]Costs in 2011 US dollars.
PDC indicates proportion of days covered; SD, standard deviation.

comorbidity index, baseline adherence, type of antipsychotics received, and past healthcare costs. The covariates considered for the logistic regression models evaluating the likelihood of achieving the HEDIS continuity of antipsychotic measure were selected from data elements available on claims from the baseline year. *P* values testing the difference between patients receiving paliperidone palmitate and those receiving any other antipsychotic medication and 95% confidence intervals (CIs) were calculated.

Furthermore, 2 additional multivariate logistic regression models were conducted to assess the robustness of the findings, including a weighted multivariate logistic regression with the model not truncated, and a multivariate logistic regression without inverse probability of treatment weights adjustment.

All statistical analyses were conducted using SAS version 9.3 (SAS Institute, Inc; Cary, NC).

## Results

A total of 492 patients were selected for the paliperidone palmitate cohort and 12,498 were selected for the other antipsychotics (eg, quetiapine, risperidone, and haloperidol). **Figure 2** outlines the sample selection process. **Table 1** presents the baseline-year demographics and the clinical characteristics of the study population, as well as the stratification of the 2 treatment cohorts.

The mean age of the study population was 46.4 years, and 46.1% were women. The patients who received paliperidone palmitate were significantly different from the patients who received other antipsychotics in terms of age, race, state, and Quan Charlson Comorbidity Index (*P* <.001 for all). There were differences in some annual healthcare cost categories, such as pharmacy costs ($9662 vs $6738, respectively; *P* <.001); inpatient costs ($9061 vs $4289, respectively; *P* <.001); outpatient costs ($2551 vs $6463, respectively; *P* <.001); and mental institution costs ($5522 vs $3179, respectively; *P* <.001).

Of the 12,990 patients who received antipsychotics, 48.6% successfully achieved the criteria for antipsychotic drug continuity in the measurement year (**Table 2**). Among the adherent patients during the baseline year, 76.2% met the continuity criteria in the measurement

**Table 2** Comparison of Goal Achievement of Adherence, by Baseline Adherence Status and Type of Antipsychotic Drug

| Adherence status at baseline, N (%) | | | | | | | |
|---|---|---|---|---|---|---|---|
| | All patients | | Baseline PDC ≥0.8 | | Baseline PDC <0.8 | | |
| Patients | All users, N | Achievers,[a] N (%) | All users, N | Achievers,[a] N (%) | All users, N | Achievers,[a] N (%) | *P* value[b] |
| Paliperidone palmitate users | 492 | 228 (46.3) | 197 | 150 (76.1) | 295 | 78 (26.4) | <.0001 |
| Other antipsychotic drug users | 12,498 | 6088 (48.7) | 5459 | 4161 (76.2) | 7039 | 1927 (27.4) | <.0001 |
| Total | 12,990 | 6316 (48.6) | 5656 | 4311 (76.2) | 7334 | 2005 (27.3) | <.0001 |
| **Type of antipsychotic drug users at baseline, N (%)** | | | | | | | |
| | All patients | | Paliperidone palmitate users | | Other antipsychotics users | | |
| PDC | All users, N | Achievers,[a] N (%) | All users, N | Achievers,[a] N (%) | All users, N | Achievers,[a] N (%) | *P* value[b] |
| Baseline PDC ≥0.8 | 5656 | 4311 (76.2) | 197 | 150 (76.1) | 5459 | 4161 (76.2) | .9792 |
| Baseline PDC <0.8 | 7334 | 2005 (27.3) | 295 | 78 (26.4) | 7039 | 1927 (27.4) | .7240 |
| Total | 12,990 | 6316 (48.6) | 492 | 228 (46.3) | 12,498 | 6088 (48.7) | .3022 |

[a]Achievers were identified as patients with a PDC ≥80% during the measurement year.
[b]Statistical differences between cohorts were calculated using chi-square tests.
PDC indicates proportion of days covered.

year, as opposed to 27.3% of the nonadherent patients during the baseline year (*P* <.001).

The success rates on the continuity measure were similar between the paliperidone palmitate (46.3%) cohort and the other antipsychotics cohort (48.7%; *P* = .302).

The **Figure** in the **Appendix** (see www.AHDBonline.com) shows the distribution of the propensity score, and **Table 2** in the **Appendix** shows the truncated and not truncated inverse probability of treatment weights. The propensity scores ranged from >0 to 0.4317 in the paliperidone palmitate cohort and from >0 to 0.4284 in the oral antipsychotics cohort; the truncated weights ranged from 1.15 to 12.97 in the paliperidone palmitate cohort and from 0.50 to 0.87 in the oral antipsychotics cohort.

After controlling for other covariates, the odds of success for the HEDIS continuity measure were increased with increased adherence during baseline (OR, 9.42; 95% CI, 8.55-10.39), female sex (OR, 1.11; 95% CI, 1.01-1.22), age 55 to 64 years (OR, 1.26; 95% CI, 1.09-1.46) relative to age 25 to 34 years old, and Hispanic ethnicity (OR, 1.37; 95% CI, 1.05-1.81) relative to white ethnicity (**Table 3**).

An increase in baseline inpatient admission cost was also associated with greater odds of success (increase of $10,000; OR, 1.11; 95% CI, 1.08-1.15). Accounting for the baseline differences between the 2 treatment cohorts using inverse probability of treatment weights, receiving paliperidone palmitate during the baseline year was associated with a 26% increase in the odds of achieving medication continuity compared with receiving other antipsychotics (OR, 1.26; 95% CI, 1.14-1.39). Similar trends were found when controlling with inverse probability of treatment weights but without truncating weights (sensitivity 1, OR, 1.36; 95% CI, 1.25-1.49), and when not controlling with the inverse probability of treatment weights (sensitivity 2, OR, 1.21; 95% CI, 0.98-1.49).

## Discussion

This study is based on real-world claims data of patients with Medicaid coverage and using antipsychotic medication for schizophrenia. Approximately 50% of the study population successfully achieved the criteria for antipsychotic drug continuity. Among the characteristics observed in the administrative claims, the factors that were significantly associated with adherence to the HEDIS measure were identified. Older age, female sex, Hispanic ethnicity, the previous-year adherence, higher inpatient costs, and the use of paliperidone palmitate therapy were predictive factors for attaining adherence to the HEDIS measure in the measurement year.

Several studies have evaluated the consequences of nonadherence to medication among patients with schizophrenia.[9,35-37] The negative impact of nonadherence on the course of illness includes increased relapses, an increase in rehospitalizations, and an increased risk for suicide attempts.[36,38] The cost of nonadherence was estimated to range from $1.4 million to $1.8 million in

**Table 3** Predictors of Adherence Goal Achievement Among Antipsychotics Users at Baseline[a]

| Predictor | Base-case model Multivariate logistic regression with truncated IPTW | | Sensitivity 1 Multivariate logistic regression with IPTW, no truncation | | Sensitivity 2 Multivariate logistic regression | |
|---|---|---|---|---|---|---|
| | Odds ratio (95% CI) | P value[b] | Odds ratio (95% CI) | P value[b] | Odds ratio (95% CI) | P value[b] |
| Baseline year adherence status | | | | | | |
| PDC ≥0.8 | 9.42 (8.55-10.39) | <.0001 | 10.50 (9.54-11.56) | <.0001 | 8.77 (8.03-9.59) | <.0001 |
| Type of antipsychotic used | | | | | | |
| *Baseline year* | | | | | | |
| Paliperidone palmitate users | 1.26 (1.14-1.39) | <.0001 | 1.36 (1.25-1.49) | <.0001 | 1.21 (0.98-1.49) | .0772 |
| Other antipsychotics users | Reference | | Reference | | Reference | |
| *Year before baseline* | | | | | | |
| Other antipsychotics users | 0.78 (0.65-0.92) | .0041 | 0.91 (0.77-1.07) | .2617 | 0.83 (0.71-0.97) | .0160 |
| Untreated patients | Reference | | Reference | | Reference | |
| *2 years before baseline* | | | | | | |
| Any antipsychotics users | 1.64 (1.42-1.88) | <.0001 | 1.34 (1.17-1.53) | <.0001 | 1.36 (1.20-1.54) | <.0001 |
| Untreated patients | Reference | | Reference | | Reference | |
| Age-categories, yrs | | | | | | |
| 25-34 | Reference | | Reference | | Reference | |
| 35-44 | 0.91 (0.79-1.05) | .183 | 1.04 (0.91-1.20) | .5467 | 0.96 (0.84-1.10) | .5578 |
| 45-54 | 1.00 (0.87-1.14) | .964 | 1.00 (0.88-1.14) | .9972 | 1.08 (0.96-1.22) | .2031 |
| 55-64 | 1.26 (1.09-1.46) | .0017 | 1.60 (1.39-1.85) | <.0001 | 1.25 (1.10-1.43) | .0009 |
| Female sex | 1.11 (1.01-1.22) | .0275 | 0.90 (0.82-0.98) | .0154 | 1.13 (1.04-1.22) | .0049 |
| Race | | | | | | |
| White | Reference | | Reference | | Reference | |
| Black | 1.01 (0.91-1.12) | .9128 | 0.91 (0.83-1.01) | .0779 | 1.01 (0.91-1.11) | .9110 |
| Hispanic | 1.37 (1.05-1.81) | .0219 | 4.38 (3.42-5.64) | <.0001 | 1.20 (0.99-1.46) | .0676 |
| Other | 1.25 (1.05-1.48) | .0104 | 0.70 (0.60-0.82) | <.0001 | 1.37 (1.18-1.59) | <.0001 |
| Unknown | 1.23 (0.64-2.40) | .5369 | 1.03 (0.55-1.98) | .9199 | 0.90 (0.51-1.58) | .7092 |
| State | | | | | | |
| Florida | Reference | | Reference | | Reference | |
| Iowa | 0.70 (0.49-1.02) | .0619 | 1.27 (0.93-1.72) | .1283 | 0.52 (0.39-0.69) | <.0001 |
| Kansas | 0.42 (0.33-0.55) | <.0001 | 0.55 (0.43-0.70) | <.0001 | 0.36 (0.28-0.45) | <.0001 |
| Missouri | 0.22 (0.18-0.26) | <.0001 | 0.33 (0.28-0.39) | <.0001 | 0.21 (0.18-0.24) | <.0001 |
| New Jersey | 0.36 (0.30-0.44) | <.0001 | 0.49 (0.41-0.57) | <.0001 | 0.42 (0.37-0.48) | <.0001 |
| Quan Charlson Comorbidity Index | 1.00 (0.97-1.03) | .9109 | 0.97 (0.94-0.99) | .0127 | 0.98 (0.96-1.01) | .1872 |
| Healthcare costs[c] | | | | | | |
| Baseline year | | | | | | |
| Medical | | | | | | |
| Inpatient | 1.11 (1.08-1.15) | <.0001 | 1.12 (1.08-1.15) | <.0001 | 1.07 (1.04-1.10) | <.0001 |
| Outpatient | 1.05 (1.00-1.09) | .0513 | 1.14 (1.08-1.20) | <.0001 | 1.04 (1.01-1.08) | .0115 |
| Emergency department costs[d] | 0.94 (0.88-1.01) | .1018 | 0.96 (0.90-1.04) | .3145 | 0.91 (0.86-0.96) | .0006 |

*Continued*

**Table 3** Predictors of Adherence Goal Achievement Among Antipsychotics Users at Baseline[a] *(Continued)*

| Predictor | Base-case model Multivariate logistic regression with truncated IPTW | | Sensitivity 1 Multivariate logistic regression with IPTW, no truncation | | Sensitivity 2 Multivariate logistic regression | |
|---|---|---|---|---|---|---|
| | Odds ratio (95% CI) | *P* value[b] | Odds ratio (95% CI) | *P* value[b] | Odds ratio (95% CI) | *P* value[b] |
| Home visit costs | 1.01 (0.95-1.08) | .7167 | 0.92 (0.87-0.98) | .0056 | 1.06 (0.99-1.13) | .0896 |
| Long-term care costs | 1.16 (1.08-1.24) | <.0001 | 1.13 (1.06-1.21) | .0002 | 1.15 (1.09-1.21) | <.0001 |
| Mental institute costs | 0.99 (0.94-1.04) | .6753 | 1.00 (0.95-1.06) | .9692 | 0.98 (0.93-1.02) | .3559 |
| Other costs | 1.05 (0.97-1.13) | .2355 | 1.04 (0.96-1.12) | .3270 | 0.94 (0.87-1.01) | .0856 |
| Year before baseline | | | | | | |
| Medical costs | | | | | | |
| Inpatient costs | 1.07 (1.03-1.10) | <.0001 | 1.07 (1.03-1.10) | <.0001 | 1.03 (1.01-1.06) | .0107 |
| Outpatient costs | 0.98 (0.94-1.02) | .2592 | 0.96 (0.93-1.00) | .0536 | 0.99 (0.96-1.01) | .3289 |
| Emergency department costs[d] | 1.00 (0.95-1.04) | .8827 | 1.03 (0.98-1.07) | .2613 | 0.98 (0.94-1.02) | .3170 |
| Home visit costs | 1.08 (0.98-1.22) | .1836 | 1.14 (1.02-1.28) | .0280 | 1.03 (0.96-1.14) | .5410 |
| Long-term care costs | 1.07 (1.04-1.12) | .0004 | 1.11 (1.06-1.16) | <.0001 | 1.04 (1.02-1.06) | .0008 |
| Mental institute costs | 0.99 (0.95-1.03) | .6704 | 0.99 (0.95-1.03) | .4823 | 0.99 (0.96-1.02) | .4394 |
| Other costs | 0.98 (0.93-1.03) | .4457 | 0.95 (0.90-1.00) | .0524 | 0.97 (0.93-1.01) | .1979 |
| 2 years before baseline | | | | | | |
| Medical costs | | | | | | |
| Inpatient costs | 0.99 (0.95-1.02) | .4148 | 0.98 (0.95-1.01) | .2177 | 0.99 (0.96-1.01) | .3018 |
| Outpatient costs | 1.04 (0.99-1.09) | .1187 | 1.28 (1.23-1.33) | <.0001 | 1.01 (0.98-1.04) | .4806 |
| Emergency department costs[d] | 0.96 (0.91-1.01) | .1288 | 0.94 (0.90-0.99) | .0202 | 1.00 (0.97-1.04) | .8037 |
| Home visit costs | 0.85 (0.76-0.96) | .0093 | 0.87 (0.77-0.97) | .0173 | 0.97 (0.89-1.06) | .5650 |
| Long-term care costs | 1.05 (1.03-1.08) | <.0001 | 1.09 (1.07-1.11) | <.0001 | 1.02 (1.01-1.04) | .0069 |
| Mental institute costs | 1.02 (0.99-1.06) | .1234 | 1.02 (0.99-1.05) | .2835 | 1.02 (0.99-1.04) | .1819 |
| Other costs | 1.00 (0.96-1.04) | .9709 | 1.00 (0.96-1.03) | .9290 | 1.00 (0.97-1.04) | .8330 |

[a]Achievers were identified as patients with a PDC ≥80% during the measurement year.
[b]Statistical significance calculated using a chi-square test obtained from logistic regression.
[c]Expressed per $10,000 increments in 2011 US dollars. Emergency department cost is expressed per $1000 increments. For patients with missing data before the baseline period, the costs have been extrapolated using baseline and nonmissing cost information.
[d]Expressed per $1000 increments in 2011 US dollars.
CI indicates confidence interval; IPTW, inverse probability of treatment weights; PDC, proportion of days covered.

the United States for 2005.[39] Therefore, full adherence to medication is a key factor among patients with schizophrenia.

Recent meta-analyses suggest mixed results regarding the effectiveness of long-acting injectable antipsychotics compared with oral antipsychotics when analyzing randomized controlled trials,[23,24] but long-acting injectable antipsychotics were superior to oral antipsychotics in observational retrospective studies.[24-28] Kirson and colleagues suggest that although randomization is considered the gold standard to eliminating selection bias in estimating treatment effects, the randomized clinical trial setting does not reflect other aspects of the way therapies are used in general clinical practice.[27]

For example, clinical trials may have more frequent protocol-dictated medical visits and drug use controls than in the real-world setting, which may influence patients' adherence to their treatment (ie, the Hawthorne effect).[40] Real-world studies using methods to control for confounding bias, such as inverse probability of treatment weights, are warranted to assess the association between treatment and adherence in the general

clinical practice, although they can only control for observable parameters.

The results of our current study add to the previous literature based on real-world data that taking paliperidone palmitate is associated with a 26% increase in the odds of achieving adherence to an antipsychotic medication (ie, the HEDIS continuity measure; OR, 1.26; 95% CI, 1.14-1.39) compared with taking other antipsychotic drugs. However, patients receiving paliperidone palmitate had higher inpatient and mental institution costs in the baseline year, which may be indicative of a different level of care in the measurement year, and this, in turn, could have affected their adherence.

Another important finding of our study is the role of baseline adherence on future adherence in a population of Medicaid-insured patients with schizophrenia. Previous studies already established this relationship in populations with and without Medicaid insurance.[41-43] In a Medicaid-insured population, nonadherence to therapy was found to significantly increase the likelihood of future nonadherence by 12-fold.[43] This is in line with the results of our study, in which adherence to therapy significantly increased the odds of future adherence by 9-fold, emphasizing the importance of factors other than medication type in determining adherence. This suggests that patient characteristics and other dimensions influencing medication adherence can outweigh the impact of the type of medication used to control the symptoms of psychoses.

We found little difference in the crude success rates observed for the paliperidone palmitate and the other antipsychotics cohort. Table 2 demonstrates how a single patient characteristic—the previous-year adherence—can affect adherence, highlighting the need to control for confounding factors among treatment cohorts.

Given the variability in patient characteristics, the inverse probability of treatment weights was widely distributed. In the main analysis, the lowest and highest weights were truncated to first or 99% of the weight distribution. In sensitivity analysis 1, incorporating untruncated weights, the effects of baseline adherence and the use of paliperidone palmitate were even greater. Sensitivity analysis 2 compared the propensity score–matched cohorts without weighting to adjust for potential treatment confounders and found similar results, although the effect of the use of paliperidone palmitate was no longer significant ($P = .0772$).

To our knowledge, the current study is the first evaluation of the predictive factors of adherence (as defined by HEDIS) in patients identified as the target population according to HEDIS. Therefore, the results of this study provide meaningful insight for Medicaid plans in their efforts to improve the quality of care for patients with schizophrenia.

## Limitations

The current study was subject to certain limitations. The Medicaid data used in this study came from only 5 states and may not be representative of the entire US population, of other states, or of non–Medicaid-covered patients.

Furthermore, the data, coming from real-world claims, were subject to billing inaccuracies and missing data as all data are.

The population sample analyzed for the HEDIS measure was identified based on the NCQA guidelines, but it may not be fully representative of the general Medicaid-covered patient population, because the presence of healthcare claims limits the analysis to patients who are already engaged in the healthcare system.

Claims-based adherence measures (eg, the PDC) do not account for whether the drugs dispensed were taken as prescribed. This may overestimate patient adherence, especially for patients taking an oral antipsychotic medication, for whom we assumed that they took their medication correctly (eg, 1 pill daily), whereas for paliperidone palmitate, the duration of effect for 1 injection is independent of any further action by the patient.

The group of patients who received other antipsychotic drugs encompassed a wide variety of medications, including oral and long-acting injectable typical and atypical antipsychotics, with potentially different adherence profiles. The mix of other antipsychotic drugs could alter the effect that is specifically attributable to paliperidone palmitate.

As with any observational studies, the study groups may differ in terms of disease severity or other characteristics at baseline that are known to be prognostically important.

Finally, we used propensity scoring and inverse probability of treatment weights to control for population differences based on the information that was available in the database. Similarly, the potential predictors of the HEDIS continuity of antipsychotics measure were limited to the factors observable on the Medicaid claims. Important factors, such as socioeconomic status, alcohol or drug use, disease severity (eg, the Positive and Negative Syndrome Scale), attitude toward illness and medication, and provider or family support, may also be important determinants of treatment choice or HEDIS performance but are not observable through administrative claims databases. Nevertheless, health insurance claims data remain a valuable tool for population health decision makers because of the relevant information on patient characteristics and outcomes and the typically large volume of data from a real-world setting.

## Conclusion

Of the information available in the database, the baseline factors that were associated with better performance on the continuity of antipsychotic medications measure

included older age, female sex, Hispanic ethnicity, previous-year adherence, higher inpatient costs, and the use of paliperidone palmitate therapy. These findings offer insight into the effects that patient characteristics and treatment types have on adherence among patients with schizophrenia. Although more research is needed, this information may help healthcare plans that cover Medicaid populations to better address the quality of care provided to Medicaid patients with schizophrenia. ■

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*Stakeholder Perspective next page*

STAKEHOLDER PERSPECTIVE

# Patient Characteristics, Adherence, and a Metric of Organizational Performance in Behavioral Health

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Although the clinical presentation of schizophrenia varies, chronicity, disturbances in thought and perceptions, and multidisciplinary approaches to patient management are ubiquitous. Factors related to medication adherence and costs suggest that antipsychotic medication use can improve outcomes in selected patients. Lafeuille and colleagues examine patient adherence to a long-acting injectable (LAI) antipsychotic medication within a Medicaid population using a retrospective longitudinal cohort design with calendar year baseline and measurement periods.[1] Based on the HEDIS measure of continuity of antipsychotic use, their results identify a subset of patients for a therapeutic stratagem yielding important outcomes, and support the utility of a common metric to assess organizational performance in schizophrenia treatment.

**RESEARCHERS:** Adherence to antipsychotic agents in patients with schizophrenia varies considerably across studies.[2] Mixed results with LAI antipsychotic use versus oral agents in terms of symptomatology and healthcare utilization are common,[3] but aggregate data indicate that patients benefit from LAI antipsychotics when adherence to oral therapy is difficult.

Randomized controlled trials (RCTs) are often uninformative in this regard because of patient eligibility criteria that exclude nonadherent patients and other design criteria of RCTs.[4] When these criteria are relaxed, variables for adherent and nonadherent groups can be defined. Medical and pharmacy claims from Medicare databases permit examination of age, sex, race, region, comorbidities, and antipsychotic type and regimen as predictors of adherence. By adjusting for potential confounders, estimates of the relative importance of each variable on adherence and outcomes inform patient care.[5] Well-controlled, innovative prospective studies in schizophrenia examining the impact of LAI on symptomatology and outcomes[6] complement conclusions from observational research. Both yield converging evidence that LAI antipsychotics is an independent determinant of clinical symptomatology and healthcare utilization in a subset of patients.

**PAYERS:** Significant regional variations in LAI prescribing rates exist.[7] Establishing a quality metric across diverse networks, using easily derived, common parameters to assess quality of care in mental health are supported by various professional associations and independent organizations with behavioral health focus. Identification of patient factors dictating medication adherence are noteworthy within this mosaic, and increases in inpatient and outpatient healthcare utilization are substantial with even nominal gaps in therapy.[8] When comparing all sources of expenditures, a potential benefit in a subset of patients is discerned comparing LAI medication cost versus hospitalization and the intensive case management associated with psychotic relapse. Risk stratification for nonadherence based on patient variables provides a focus for physician and patient education, and cost control.

**PATIENTS:** Successful management of patients with schizophrenia requires a blend of pharmacologic and psychosocial interventions. Treatment regimens are complex and patient adherence is complicated by potential cognitive disturbances and other environmental factors.[9] Although the use of LAI antipsychotics alone cannot explain all variance in outcomes, identifying patients who could benefit from LAI medication use directs LAI therapy to the most appropriate patients, facilitating processes of social reintegration. ■

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## Appendix

**Factors Associated with Performance on HEDIS Adherence Quality Measure in Schizophrenia Population**

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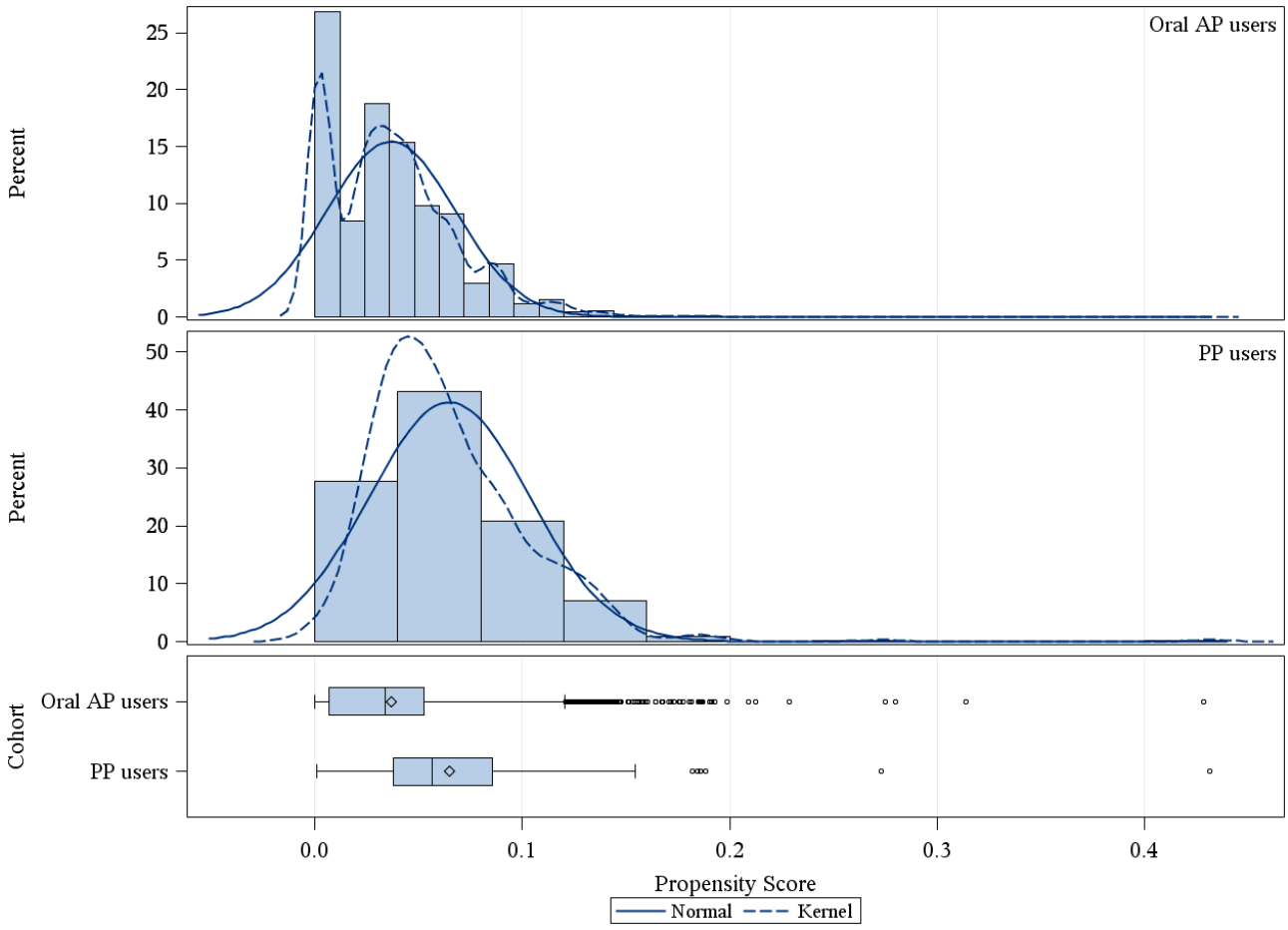
NOTE: This Appendix has not been edited and is provided as supplemental materials for this article, which was published in *American Health & Drug Benefits* in October 2016.

**Figure Distribution of Propensity Score**[a]




[a]The propensity score was based on the conditional probability of a patient being treated with PP. Covariates included in the logistic regression were age, gender, race, state, and 1-year and 2-year lags in baseline costs.

**Appendix Table 1. List of antipsychotics used among patients using other antipsychotics than paliperidone palmitate**

| Type of antipsychotics[a] | Other antipsychotic drug users, N (%) (N = 12,498) |
|---|---|
| Quetiapine | 4,056 (32.5%) |
| Risperidone | 3,684 (29.5%) |
| Haloperidol | 2,802 (22.4%) |
| Aripiprazole | 2,635 (21.1%) |
| Olanzapine | 2,587 (20.7%) |
| Ziprasidone | 1,488 (11.9%) |
| Clozapine | 1,002 (8.0%) |
| Paliperidone | 981 (7.8%) |
| Risperidone injectable | 835 (6.7%) |
| Fluphenazine | 716 (5.7%) |
| Fluphenazine injectable | 511 (4.1%) |
| Chlorpromazine | 503 (4.0%) |
| Haloperidol injectable | 377 (3.0%) |
| Perphenazine | 362 (2.9%) |
| Thiothixene | 196 (1.6%) |
| Prochlorperazine | 195 (1.6%) |
| Asenapine injectable | 181 (1.4%) |
| Iloperidone | 144 (1.2%) |
| Loxapine | 144 (1.2%) |
| Trifluoperazine | 130 (1.0%) |
| Thioridazine | 94 (0.8%) |
| Olanzapine injectable | 62 (0.5%) |
| Chlorpromazine injectable | 59 (0.5%) |
| Prochlorperazine injectable | 30 (0.2%) |
| Aripiprazole injectable | 17 (0.1%) |

| | |
|---|---|
| Molindone | 14 (0.1%) |
| Pimozide | 2 (0.0%) |

[a]As patients may use more than one antipsychotic medication during the baseline period, the categories are not mutually exclusive.

**Table 2. Distribution of IPTWs**

| | **Truncated IPTW[a,b]** | | **Not truncated IPTW** | |
|---|---|---|---|---|
| | **Paliperidone palmitate users (Effective N = 4,352)** | **Other antipsychotic drug users (Effective N = 6,431)** | **Paliperidone palmitate users (Effective N = 4,352)** | **Other antipsychotic drug users (Effective N = 6,431)** |
| **Mean** | 8.8449 | 0.5145 | 13.3327 | 0.5145 |
| **Distribution** | | | | |
| Minimum | 1.1466 | 0.4953 | 1.1466 | 0.4950 |
| 1st percentile | 2.6869 | 0.4953 | 2.6869 | 0.4953 |
| 5th percentile | 3.7700 | 0.4957 | 3.7700 | 0.4957 |
| 25th percentile | 5.7802 | 0.4984 | 5.7802 | 0.4984 |
| 50th percentile (median) | 8.7582 | 0.5123 | 8.7582 | 0.5123 |
| 75th percentile | 12.9670 | 0.5224 | 13.0638 | 0.5224 |
| 95th percentile | 12.9670 | 0.5439 | 22.9272 | 0.5439 |
| 99th percentile | 12.9670 | 0.5672 | 170.0816 | 0.5672 |
| Maximum | 12.9670 | 0.8660 | 526.8319 | 0.8660 |

IPTW: inverse probability of treatment weights.
[a]Weights were obtained using the propensity score based on the conditional probability of a patient being treated with paliperidone palmitate.
[b]To avoid the influence of high weights on the results, weights were truncated at 1% and 99% of the pooled weight distribution.