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ORIGINAL RESEARCH

Real-World Adherence and Discontinuation of Oral Antipsychotics and Associated Factors in a National Sample of US Medicare Beneficiaries with Schizophrenia

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Purpose: Little is known about adherence to and discontinuation of newly initiated oral antipsychotics (OAPs) as well as associated factors among Medicare beneficiaries with schizophrenia. This study aimed to examine rates of OAP adherence and discontinuation and associated factors in a national sample of fee-for-service Medicare beneficiaries with schizophrenia.

Patients and Methods: This retrospective study used 100% fee-for-service Medicare claims data to identify adult beneficiaries with schizophrenia, initiating a new OAP between 01/01/2017 and 12/31/2019 (index date = date of new OAP prescription). Outcomes included adherence and discontinuation. Factors associated with adherence were assessed using logistic and linear regressions; Cox regressions were used to assess factors associated with discontinuation.

Results: In our final sample of 46,452 Medicare beneficiaries with schizophrenia, 35.4% were adherent to their newly initiated OAP (mean [SD] PDC: 0.52 [0.37]) over 12 months after initiation. Most patients (79.4%) discontinued their new OAP (median [IQR] time to discontinuation: 3.6 (1.0, 9.9) months). Factors associated with lower odds of adherence included younger age (OR: 0.43; 95% CI: 0.40–0.47, p <0.001 for patients aged 18–35 relative to patients aged ≥65 years); non-White race (OR: 0.72; 95% CI: 0.69–0.75, p <0.001 relative to White patients); and evidence of prior schizophrenia-related hospitalization (OR: 0.80; 95% CI: 0.77–0.83, p <0.001 relative to patients without evidence of prior schizophrenia-related hospitalization). Similar associations were observed for discontinuation outcomes. Twice-daily dosing frequency was also associated with lower odds of adherence (odds ratio [OR]: 0.93; 95% CI: 0.89–0.97, p = 0.0014) and higher hazard of discontinuation (hazard ratio [HR]: 1.03; 95% CI: 1.00–1.05, p = 0.0244) relative to once-daily dosing frequency.

Conclusion: We found high rates of non-adherence and discontinuation among Medicare beneficiaries initiated on currently available OAPs. We also identified risk factors that contribute to increased odds of medication non-adherence. By identifying at-risk patient populations, targeted interventions can be initiated to facilitate treatment continuity.

Plain Language Summary: Although half of patients with schizophrenia are covered by Medicare, little is known about how consistently they take their antipsychotic medications, which is a crucial part of successful treatment. We found that only 1/3 of Medicare beneficiaries consistently took their medications and nearly 80% discontinued treatment, often shortly after starting it. Younger patients, non-White patients, and patients who had to take pills multiple times per day were less likely to consistently take their medications.

Keywords: adherence, antipsychotic, Medicare, discontinuation

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Introduction

Schizophrenia is a chronic, severe mental illness with a prevalence of approximately 1% in the United States.[1] The annual excess economic burden of schizophrenia was estimated to be approximately $343 billion in 2019, and evidence suggests that that burden is increasing.[2] Antipsychotic medications are key to the successful management of schizophrenia. Two broad classes of antipsychotic medications exist: (i) first-generation antipsychotics (FGAs, "typical antipsychotics") and (ii) second-generation antipsychotics (SGAs, "atypical antipsychotics"). Critically, while both medication classes are effective, they differ in their side effect profiles. Patients treated with older FGAs, such as haloperidol and fluphenazine, are at increased risk of extrapyramidal symptoms (EPS).[3] Patients treated with newer SGAs, such as risperidone and olanzapine, have a lower risk of EPS but higher risk of metabolic side effects.[4] Regardless of the antipsychotic agent chosen, consistent use of the medication is critical to lowering the risk of acute psychotic episodes and decreasing the frequency of relapses and psychiatric hospitalizations.[5]

Despite its importance, adherence to antipsychotic medications remains poor among patients with schizophrenia.[6,7] Prior research has shown that factors such as social isolation and stigma, comorbid substance abuse, symptom severity, and financial burden can all impact adherence.[8,9] Although the problem is clearly multifaceted, variability in the effectiveness and tolerability of individual agents often leads to a "trial-and-error" strategy with respect to treatment choice, with many patients discontinuing newly-prescribed agents shortly after initiation.[10,11] A key source of this variability and subsequent discontinuation arises due to the differing side effect profiles of currently available first- and second-generation antipsychotics.[12,13] While some side effects are severe enough to warrant discontinuation, even mild adverse events can negatively impact adherence, with serious implications for patient outcomes.[14,15]

Another potential cause of poor adherence relates to the dosing frequency of the medications given the need for individuals with schizophrenia to be on continuous lifelong treatment with antipsychotics.[16] While numerous long-acting injectable antipsychotics are presently available, the vast majority of individuals with schizophrenia still rely on daily oral antipsychotic agents as their cornerstone treatment for schizophrenia management.[17] Furthermore, among daily oral antipsychotic agents, there are varying dosing frequencies—once daily, twice daily, etc.—that can influence adherence.[16]

Previous studies have demonstrated poor real-world adherence among individuals with schizophrenia initiating oral antipsychotic treatments across the Medicaid, Veterans Affairs, and commercial insurance settings.[6,18–21] However, little real-world evidence exists concerning rates of oral antipsychotic adherence and discontinuation and associated factors in the US Medicare population. This represents a major gap in the literature given that approximately half of patients with schizophrenia in the US receive coverage via Medicare—the vast majority of whom receive oral antipsychotics[22]—and hence prior analyses have omitted this large patient population.[23] Medicare beneficiaries, often representing older or disabled adults with complex health needs, may face unique challenges in adhering to their medication regimens, including functional limitations, comorbid conditions, and cost-related barriers.[24] In addition to studying the rates of adherence to oral antipsychotics in the Medicare population, it is also important to understand factors associated with adherence in real-world clinical practice. Identifying particular groups at risk for increased odds of non-adherence will permit targeted interventions for these populations. Additionally, prescribers may benefit from such information when weighing different treatment options for patients with schizophrenia. This study fills gaps in the literature by examining rates of oral antipsychotic adherence and discontinuation and associated factors in a national sample of fee-for-service Medicare beneficiaries with schizophrenia.

Material and Methods

Study Design & Data Source

This retrospective claims-based study used an extract of 100% Chronic Conditions Data Warehouse (CCW) Medicare claims data available from the Centers for Medicare and Medicaid Services (CMS). The data extract ranged from 01/01/2016 to 12/31/2019. Although more recent data (2020–2021) were available, data prior to the COVID-19 pandemic that started in 2020 was used to more accurately reflect typical medical care received by schizophrenia patients. The CCW files contain data on all fee-for-service Medicare beneficiaries, including Medicare Parts A and Part B medical claims,

and Part D prescription claims for outpatient prescription drugs. The claims files are linked to a personal summary file with the beneficiary's demographic and enrollment information.

Sample Selection

The study sample included all fee-for-service Medicare beneficiaries with schizophrenia initiating a new oral antipsychotic agent (Appendix Table A1). Patients were included in the final sample if they had evidence of a new oral antipsychotic prescription claim between 01/01/2017 and 12/31/2018. A new oral antipsychotic was defined based on no evidence of a claim for the same oral antipsychotic agent in the previous 12 months (Note: the patient could have used other oral antipsychotic agents in the previous 12 months). The date of the first fill for the new oral antipsychotic prescription was defined as the index date and the new oral antipsychotic prescription was defined as the index agent; patients with evidence of two or more new oral antipsychotic agents on the index date were not included. Additional sample selection criteria included (1) continuous fee-for-service Medicare Part A and B coverage for 12-months before and at least 12-months after the index date, (2) continuous standalone Medicare Part D prescription drug coverage for 12-months before and at least 12-months after the index date, (3) ≥1 inpatient claim and/or ≥2 outpatient claims on different days with a diagnosis of schizophrenia (ICD-10-CM: F20.XX) in any position, (4) aged ≥18 years on index date, and (5) no evidence of a long-acting injectable (LAI) antipsychotic in the 12-month pre-index period since most patients initiated on an LAI have already been given a trial on the oral formulation of the LAI to ensure it is well-tolerated and may have historically demonstrated poor adherence necessitating the LAI.

Outcomes

The primary outcomes of interest were adherence to and discontinuation of the index oral antipsychotic agent.

Adherence to the index oral antipsychotic agent was measured over the 12-month post-index period using the proportion of days covered (PDC) method.[25] If a patient filled their next prescription for the index agent before the end of days' supply of the previous antipsychotic prescription fill for the same agent, then it was assumed that the patient finished the prior prescription before starting the new prescription and hence the start date of the next prescription fill was pushed out to adjust for the overlapping days' supply. Adherence to the index antipsychotic agent was measured both as a binary outcome (ie, patients were deemed adherent if they had a PDC ≥0.80[26,27]) and a continuous outcome (PDC score). Examining adherence as both a binary and continuous outcome allowed us to report the proportion of patient who met a minimum threshold of the proportion of days covered and could be deemed adherent as well as the mean proportion of days in the 12-month period that were covered by the index oral antipsychotic agent.

Discontinuation of the index oral antipsychotic was defined as the presence of a consecutive 60-day gap in the available days' supply of the index oral antipsychotic agent (patients who initiated a different antipsychotic were still classified as discontinuers because they discontinued treatment with their index agent). Unlike the adherence outcome that was measured over a fixed 12-month post-index period, discontinuation was assessed over the available post-index follow-up from index date until death, entry into a Medicare Advantage plan, or end of the study period, whichever occurred earlier. The time to discontinuation outcome was defined as the time from the index date to the date of discontinuation of the index drug (ie, beginning of the ≥60-day consecutive gap without the index antipsychotic agent).

Analysis

Descriptive sample characteristics were generated. The observed rates of adherence and discontinuation were reported in the overall sample. Logistic regression was used to assess the factors associated with the binary outcome of adherence (PDC ≥ 0.80). Linear regressions were used to assess factors associated with the continuous outcome of adherence (PDC score). Cox regressions were used to assess factors associated with time to discontinuation. Adjusted odds ratios (from logistic regressions) and hazard ratios (from Cox regressions) with 95% confidence intervals and p-values were presented for all the covariates.

Covariates included sociodemographic characteristics, oral antipsychotic agent characteristics, and clinical characteristics. Sociodemographic characteristics were measured on the index date and included age, sex, race, Part D low-income subsidy status, original reason for Medicare eligibility, census region, and metropolitan status. Clinical characteristics were measured in the 12-month pre-index period and included the number of Elixhauser comorbidities,[28] history of any schizophrenia-related hospitalization, and number of schizophrenia-related emergency room (ER) visits. We also

included indicators for the year in which the index antipsychotic prescription was initiated to examine any time trends in the outcomes. Finally, oral antipsychotic agent characteristics included the dosing frequency of this index antipsychotic agent (once-daily, twice-daily, thrice-daily or more) and indicators for the specific antipsychotic agent initiated (eg, risperidone, aripiprazole). Dosing frequency for the index antipsychotic was derived by dividing the quantity of pills dispensed by the days' supply field on the index prescription claim and rounding to the nearest integer. While the vast majority of antipsychotics are approved by the FDA as either once-daily or twice-daily, physicians may prescribe more frequent daily dosing for some patients. Since dosing frequency is highly correlated with the specific antipsychotic agent, our main analysis did not include indicators for the specific antipsychotic agent initiated. In sensitivity analysis, we ran the regression models with indicators for the specific index antipsychotic agent in addition to dosing frequency.

The study was deemed exempt from IRB review according to FDA 21 CFR 56.104 and 45CFR46.104(b)(4): (4) Secondary Research Uses of Data or Specimens on 02/21/2023. A Waiver of Individual Authorization under HIPAA pursuant to 45 CFR 164.512 (i)(2)(i)-(v) exempt status as specified in 45 CFR 164.512 was approved. All analyses were conducted in SAS Enterprise, Version 9.4.[29]

Results

The final sample contained 46,452 Medicare beneficiaries with schizophrenia who newly initiated an oral antipsychotic agent (Appendix Table A2). Patient sociodemographic and characteristics are reported in Table 1. The mean (SD) age of the sample was 55.0 (15.2) years and 28.5% of patients were over the age of 65 years. The sample was primarily male (55.5%), White (64.6%), receiving a Part D low-income subsidy (90.4%) and urban (82.0%). There was a significant

Table 1 Patient Characteristics

Characteristics	N	%
	46,452	**100%**
Length of available follow-up in **months** from index date[a]		
Median (IQR)	43.8 (33.1, 52.5)	
Mean (SD)	41.7 (13.2)	
Sociodemographic characteristics		
Age, mean (SD) on index date	55.0 (15.2)	
18 to 24 years	406	0.9%
25 to 34 years	4,736	10.2%
35 to 44 years	7,289	15.7%
45 to 54 years	9,123	19.6%
55 to 64 years	11,643	25.1%
≥65 years	13,255	28.5%
Sex on index date		
Male	25,768	55.5%
Female	20,684	44.5%
Race on index date		
White	29,997	64.6%
Black	11,802	25.4%
Hispanic	2,155	4.6%
Other	2,498	5.4%
Part D LIS Status on index date		
LIS	42,008	90.4%
Non-LIS	4,444	9.6%
Original reason for Medicare eligibility on index date		
Age	5,537	11.9%
Disability or ESRD[b]	40,915	87.9%

(*Continued*)

Table 1 (Continued).

Characteristics	N	%
	46,452	**100%**
Census Region on index date		
Northeast	9,107	19.6%
Midwest	10,285	22.1%
South	17,703	38.1%
West	9,357	20.1%
Metropolitan Status on index date		
Urban	38,072	82.0%
Rural	8,380	18.0%
Clinical characteristics		
Number of Elixhauser comorbidities in the 12-month pre-index period		
≤2	6,833	14.7%
3–4	10,104	21.8%
5–7	14,495	31.2%
8–10	9,274	20.0%
≥11	5,746	12.4%
Any schizophrenia-related hospitalization in the 12-month pre-index period	20,160	43.4%
Number of schizophrenia-related emergency room visits in the 12-month pre-index period		
0	33,014	71.1%
1	7,531	16.2%
2	3,006	6.5%
≥3	2,901	6.2%
All-cause healthcare costs in the 12-month pre-index period	$46,997 ($58,884)	
Schizophrenia-related healthcare costs in the 12-month pre-index period	$16,428 ($27,828)	
Oral antipsychotic agent characteristics		
Index oral antipsychotic agent on index date		
Risperidone	8,416	18.1%
Olanzapine	7,987	17.2%
Quetiapine	7,864	16.9%
Aripiprazole	5,746	12.4%
Haloperidol	4,815	10.4%
Lurasidone	2,297	4.9%
Paliperidone	1,669	3.6%
Ziprasidone	1,620	3.5%
Fluphenazine	1,037	2.2%
Other[c]	5,001	10.8%
Dosing frequency of index oral antipsychotic agent		
Once-daily	30,277	65.2%
Twice-daily	12,510	26.9%
Thrice-daily or more	3,665	7.9%
Year of index antipsychotic prescription		
2017	28,495	61.3%
2018	17,957	38.7%

Abbreviations: ESRD, end-stage renal disease; IQR, interquartile range; LIS, low-income subsidy; SD, standard deviation [a] Length of available follow-up in months from index oral antipsychotic initiation date until death, entry into MAPD, or end of study period (Dec. 31, 2019), whichever occurred earlier. [b] Only 213 (0.5%) patients in our sample had ESRD as one of the reasons for Medicare eligibility.[c] Other oral antipsychotics included asenapine, brexpiprazole, cariprazine, chlorpromazine, clozapine, iloperidone, loxapine, molindone, perphenazine, thioridazine, thiothixene, trifluoperazine, acetophenazine, chlorprothixene, mesoridazine, promazine, or triflupromazine.

comorbidity burden among these patients, with 32.5% having ≥8 Elixhauser comorbidities in the 12-months prior to initiation of their index antipsychotic agent. A large proportion of the sample (43.4%) had evidence of a schizophrenia-related hospitalization in the 12-month pre-index period; over the same period, 28.9% had evidence of ≥1 schizophrenia-related ER visits. The most common index oral antipsychotics were risperidone (18.1%), olanzapine (17.2%), quetiapine (16.9%), aripiprazole (12.4%), and haloperidol (10.4%). Most patients (65.2%) had a once-daily dosing frequency, followed by twice daily (26.9%) and thrice daily or more (7.9%).

Figure 1 reports unadjusted rates of adherence to and discontinuation of the index oral antipsychotic agent. The overall adherence rate over 12 months after the index date was 35.4%; the mean (SD) PDC was 0.52 (0.37) and the median (IQR) PDC was 0.47 (0.13, 0.95). Over a median follow-up of >43 months (3.6 years) from the index date, the rate of discontinuation of the index oral antipsychotic agent was 79.4%. The mean (SD) and median (IQR) time to discontinuation among discontinuers was 7.8 (9.9) months and 3.6 (1.0, 9.9) months, respectively.

The logistic regression results for factors associated with adherence to the index oral antipsychotic agent are reported in Table 2. With respect to sociodemographic characteristics, younger age was negatively correlated with adherence; for instance, compared to patients ≥65 years, patients who were 18 to 34 years old had significantly lower odds of adherence (OR: 0.43; 95% CI: 0.40–0.47, $p < 0.001$). Male patients had higher odds of adherence than female patients (OR: 1.08; 95% CI: 1.03–1.12, $p = 0.003$) and Black patients had lower odds of adherence than White patients (OR: 0.72; 95% CI: 0.69–0.75, $p < 0.001$). Patients not receiving a Part D low-income subsidy had lower odds of adherence relative to full LIS patients (OR: 0.77; 95% CI: 0.72–0.82, $p < 0.001$). Relative to patients located in the Northeast, patients residing in other census regions had lower odds of adherence: Midwest (OR: 0.89; 95% CI: 0.84–0.95, $p < 0.001$), South (OR: 0.82; 95% CI: 0.78–0.87, $p < 0.001$), West (OR: 0.76; 95% CI: 0.72–0.81, $p < 0.001$). Additionally, patients who resided in a rural area had higher odds of adherence (OR: 1.05; 95% CI: 1.00–1.11, $p < 0.05$) compared to patients who lived in an urban area.

Multiple clinical characteristics had an impact on the odds of adherence. In general, patients with a larger number of Elixhauser comorbidities in the 12-month pre-index period had higher odds of adherence relative to patients with ≤2 Elixhauser comorbidities: 5–7 (OR: 1.13; 95% CI: 1.06–1.20, $p < 0.001$), 8–10 (OR: 1.15; 95% CI: 1.07–1.23, p <

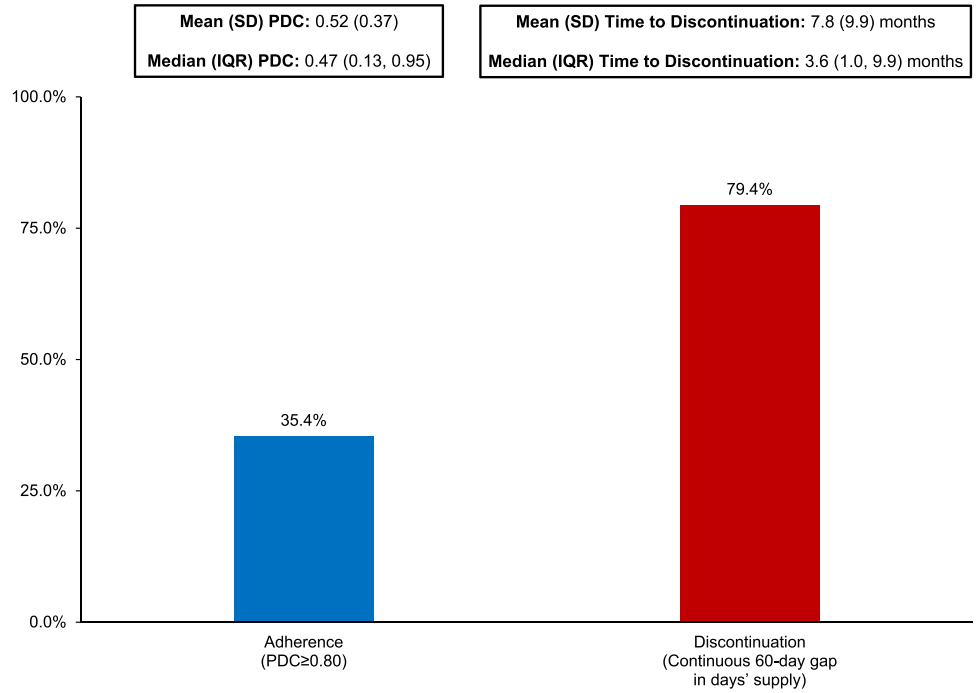

Figure 1 Observed rates of adherence (over 12-months post-index) to and discontinuation of index oral antipsychotic agent among Medicare beneficiaries with schizophrenia.

Abbreviations: IQR, interquartile range; PDC, proportion of days covered; SD, standard deviation.

Table 2 Logistic Regression Results for Factors Associated with Adherence to Index Oral Antipsychotic Agent Among Medicare Beneficiaries with Schizophrenia

Characteristic	OR	95% CI		p-value
Age on index date				
18 to 34 years	0.43	0.40	0.47	<0.0001
35 to 44 years	0.48	0.45	0.52	<0.0001
45 to 54 years	0.57	0.53	0.61	<0.0001
55 to 64 years	0.74	0.70	0.79	<0.0001
≥65 years	REF			
Sex on index date				
Male	1.08	1.03	1.12	0.0003
Female	REF			
Race on index date				
White	REF			
Black	0.72	0.69	0.75	<0.0001
Hispanic	0.77	0.69	0.85	<0.0001
Other	0.95	0.87	1.04	0.2569
Part D LIS Status on index date				
LIS	REF			
Non-LIS	0.77	0.72	0.82	<0.0001
Original reason for Medicare eligibility on index date				
Age	REF			
Disability or ESRD	1.05	0.98	1.12	0.2023
Census Region on index date				
Northeast	REF			
Midwest	0.89	0.84	0.95	0.0002
South	0.82	0.78	0.87	<0.0001
West	0.76	0.72	0.81	<0.0001
Metropolitan Status on index date				
Urban	REF			
Rural	1.05	1.00	1.11	0.0476
Number of Elixhauser comorbidities in the 12-month pre-index period				
≤2	REF			
3–4	1.05	0.98	1.12	0.1444
5–7	1.13	1.06	1.20	0.0003
8–10	1.15	1.07	1.23	0.0002
≥11	1.13	1.04	1.23	0.0035
Any schizophrenia-related hospitalization in the 12-month pre-index period	0.80	0.77	0.83	<0.0001
Number of schizophrenia-related emergency room visits in the 12-month pre-index period				
0	REF			
1	0.87	0.82	0.92	<0.0001
2	0.77	0.70	0.83	<0.0001
≥3	0.56	0.51	0.62	<0.0001
Dosing frequency of index oral antipsychotic agent				
Once-daily	REF			
Twice-daily	0.93	0.89	0.97	0.0014
Thrice-daily or more	0.75	0.70	0.81	<0.0001
Year of index antipsychotic prescription				
2017	REF			
2018	1.02	0.98	1.06	0.3300

Abbreviations: CI, confidence interval; ESRD, end-stage renal disease; LIS, low-income subsidy; OR, odds ratio.

0.001), ≥11 (OR: 1.13; 95% CI: 1.04–1.23, p<0.001). Patients with evidence of schizophrenia-related hospitalization in the 12-month pre-index period had lower odds of adherence (OR: 0.80; 95% CI: 0.77–0.83, p < 0.001). An increasing number of schizophrenia-related ER visits in the 12-month pre-index period was also associated with worse odds of adherence relative to patients with no evidence of prior schizophrenia-related ER visits: 1 visit (OR: 0.87; 95% CI: 0.82–0.92, p <0.001), 2 visits (OR: 0.77; 95% CI: 0.70–0.83, p < 0.001), ≥3 visits (OR: 0.56; 95% CI: 0.51–0.62, p < 0.001).

With respect to the characteristics of the index oral antipsychotic agent, dosing frequency was negatively associated with adherence. Compared to patients who initiated a once-daily antipsychotic, patients who initiated a twice-daily antipsychotic had lower odds of adherence (odds ratio [OR]: 0.93; 95% CI: 0.89–0.97, p = 0.0014). The difference was even more pronounced for patients who initiated an oral antipsychotic to be taken thrice-daily or more (OR: 0.75; 95% CI: 0.70–0.81, p < 0.001).

Table 3 reports the results of the linear regression of continuous PDC for the index oral antipsychotic agent. Consistent with our findings in Table 2, younger patient age, female sex, minority race, and certain clinical characteristics were associated with reductions in the estimated PDC. Additionally, patients receiving twice-daily dosing and thrice-daily dosing had continuous PDC scores that were lower by 0.02 (95% CI: 0.01–0.02, p < 0.001) and 0.08 (95% CI: 0.07–0.09, p < 0.001), respectively, compared to those receiving once-daily dosing for their index antipsychotic agent.

The Cox regression results for factors associated with discontinuation of the index oral antipsychotic agent are reported in Table 4. With respect to sociodemographic characteristics, younger age was associated with greater hazard of

Table 3 Linear Regression Results for Continuous PDC for Index Oral Antipsychotic Agent Among Medicare Beneficiaries with Schizophrenia

Characteristic	Coeff	95% CI		p-value
Age on index date				
18 to 34 years	−0.15	−0.16	−0.13	<0.0001
35 to 44 years	−0.13	−0.15	−0.12	<0.0001
45 to 54 years	−0.10	−0.12	−0.09	<0.0001
55 to 64 years	−0.06	−0.07	−0.04	<0.0001
≥65 years	REF			
Sex on index date				
Male	0.01	0.00	0.02	0.0030
Female	REF			
Race on index date				
White	REF			
Black	−0.05	−0.06	−0.04	<0.0001
Hispanic	−0.03	−0.05	−0.02	<0.0001
Other	0.00	−0.02	0.01	0.6410
Part D LIS Status on index date				
LIS	REF			
Non-LIS	−0.04	−0.06	−0.03	<0.0001
Original reason for Medicare eligibility on index date				
Age	REF			
Disability or ESRD	0.01	−0.01	0.02	0.3920
Census Region on index date				
Northeast	REF			
Midwest	−0.02	−0.03	−0.01	<0.0001
South	−0.03	−0.04	−0.02	<0.0001
West	−0.04	−0.05	−0.03	<0.0001
Metropolitan Status on index date				
Urban	REF			
Rural	0.01	0.00	0.02	0.0040

(*Continued*)

Table 3 (Continued).

Characteristic	Coeff	95% CI		p-value
Number of Elixhauser comorbidities in the 12-month pre-index period				
≤2	REF			
3–4	0.01	0.00	0.02	0.2250
5–7	0.02	0.01	0.03	0.0020
8–10	0.03	0.02	0.04	<0.0001
≥11	0.03	0.02	0.05	<0.0001
Any schizophrenia-related hospitalization in the 12-month pre-index period	−0.05	−0.06	−0.04	<0.0001
Number of schizophrenia-related emergency room visits in the 12-month pre-index period				
0	REF			
1	−0.03	−0.04	−0.02	<0.0001
2	−0.06	−0.07	−0.04	<0.0001
≥3	−0.10	−0.11	−0.09	<0.0001
Dosing frequency of index oral antipsychotic agent				
Once-daily	REF			
Twice-daily	−0.02	−0.02	−0.01	<0.0001
Thrice-daily or more	−0.08	−0.09	−0.07	<0.0001
Year of index antipsychotic prescription				
2017	REF			
2018	0.00	−0.01	0.01	0.8370

Abbreviations: CI, confidence interval; ESRD, end-stage renal disease; LIS, low-income subsidy; OR, odds ratio.

Table 4 Cox Regression Results for Factors Associated with Time to Discontinuation of Index Oral Antipsychotic Agent Among Medicare Beneficiaries with Schizophrenia

Characteristic	HR	95% CI		p-value
Age on index date				
18 to 34 years	1.51	1.45	1.58	<0.0001
35 to 44 years	1.42	1.37	1.48	<0.0001
45 to 54 years	1.32	1.28	1.37	<0.0001
55 to 64 years	1.16	1.12	1.20	<0.0001
≥65 years	REF			
Sex on index date				
Male	0.96	0.94	0.98	0.0002
Female	REF			
Race on index date				
White	REF			
Black	1.15	1.13	1.18	<0.0001
Hispanic	1.11	1.06	1.17	<0.0001
Other	1.03	0.99	1.08	0.1584
Part D LIS Status on index date				
LIS	REF			
Non-LIS	1.12	1.08	1.16	<0.0001
Original reason for Medicare eligibility on index date				
Age	REF			
Disability or ESRD	0.96	0.92	1.00	0.0361
Census Region on index date				
Northeast	REF			
Midwest	1.09	1.05	1.12	<0.0001
South	1.12	1.09	1.15	<0.0001
West	1.17	1.13	1.21	<0.0001

(*Continued*)

Table 4 (Continued).

Characteristic	HR	95% CI		p-value
Metropolitan Status on index date				
Urban	REF			
Rural	0.97	0.95	1.00	0.0531
Number of Elixhauser comorbidities in the 12-month pre-index period				
≤2	REF			
3–4	0.97	0.94	1.01	0.1156
5–7	0.94	0.91	0.97	0.0002
8–10	0.91	0.88	0.94	<0.0001
≥11	0.87	0.84	0.91	<0.0001
Any schizophrenia-related hospitalization in the 12-month pre-index period	1.12	1.10	1.15	<0.0001
Number of schizophrenia-related emergency room visits in the 12-month pre-index period				
0	REF			
1	1.08	1.05	1.11	<0.0001
2	1.16	1.12	1.21	<0.0001
≥3	1.28	1.23	1.34	<0.0001
Dosing frequency of index oral antipsychotic agent				
Once-daily	REF			
Twice-daily	1.03	1.00	1.05	0.0244
Thrice-daily or more	1.16	1.11	1.20	<0.0001
Year of index antipsychotic prescription				
2017	REF			
2018	0.98	0.96	1.00	0.0403

Abbreviations: CI, confidence interval; ESRD, end-stage renal disease; HR, hazard ratio; LIS, low-income subsidy.

discontinuation. For instance, patients who were 18 to 34 years old had a significantly higher hazard of discontinuation (HR: 1.51; 95% CI: 1.45–1.58, p < 0.001) compared to patients ≥65 years old. Male patients had lower hazard of discontinuation than female patients (HR: 0.96; 95% CI: 0.94–0.98, p < 0.001) and Black patients had greater hazard of discontinuation than White patients (HR: 1.15; 95% CI: 1.13–1.18, p < 0.001). Patients not receiving a Part D low-income subsidy had a higher hazard of discontinuation relative to full LIS patients (HR: 1.12; 95% CI: 1.08–1.16, p < 0.001). Relative to patients located in the Northeast, patients residing in other census regions had a higher hazard of discontinuation: Midwest (HR: 1.09; 95% CI: 1.05–1.12, p < 0.001), South (HR: 1.12; 95% CI: 1.09–1.15, p < 0.001), West (HR: 1.17; 95% CI: 1.13–1.21, p < 0.001).

In general, patients with a larger number of Elixhauser comorbidities in the 12-month pre-index period had a lower hazard of discontinuation relative to patients with ≤2 Elixhauser comorbidities: 5–7 (HR: 0.94; 95% CI: 0.91–0.97, p < 0.001), 8–10 (HR: 0.91; 95% CI: 0.88–0.94, p<0.001), ≥11 (HR: 0.87; 95% CI: 0.84–0.91, p<0.001). Patients with evidence of schizophrenia-related hospitalization in the 12-month pre-index period had a higher hazard of discontinuation (HR: 1.12; 95% CI: 1.10–1.15, p<0.001). An increasing number of schizophrenia-related ER visits in the 12-month pre-index period was also associated with higher hazard of discontinuation relative to patients with no evidence of prior schizophrenia-related ER visits: 1 visit (HR: 1.08; 95% CI: 1.05–1.11, p<0.001), 2 visits (HR: 1.16; 95% CI: 1.12–1.21, p<0.001), ≥3 visits (HR: 1.28; 95% CI: 1.23–1.34, p<0.001). With respect to the characteristics of the index oral antipsychotic agent, higher dosing frequency was associated with greater hazard of discontinuation of the index antipsychotic agent for both twice-daily (hazard ratio [HR]: 1.03; 95% CI: 1.00–1.05, p=0.0244) and thrice-daily or more (HR: 1.16; 95% CI: 1.11–1.20, p<0.001) antipsychotic agents.

Our sensitivity analysis results with regressions including the index antipsychotic agent are presented in Appendix Tables A3-A5. Differences in adherence and discontinuation were observed by the specific type of the index antipsychotic agent. Findings for other covariates were largely similar, though due to collinearity with dosing frequency the effect size was smaller for thrice-daily or more and no longer statistically significant for twice daily.

Discussion

Our study of US Medicare beneficiaries with schizophrenia provides one of the first real-world assessments of oral antipsychotic adherence and discontinuation in this vulnerable, under-studied population. In our sample of nearly 50,000 beneficiaries, we found that only about one-third of patients were adherent (PDC≥0.80) to their new oral antipsychotic over 12 months after treatment initiation. Furthermore, we observed that nearly 80% of patients discontinued their new oral antipsychotic medication, with a median time to discontinuation of less than 4 months. Finally, we identified multiple sociodemographic and clinical risk factors associated with lower odds of adherence and higher hazard of discontinuation.

With almost 30 agents approved for the treatment of schizophrenia, choosing a new antipsychotic for a patient may be a challenging task for clinicians. Tolerability, comorbid conditions, patient preferences, clinician experience, as well as availability, cost and health plan restrictions can all influence physicians' prescribing choice. Frequently, antipsychotic prescribing is an "trial-and-error" exercise, where one drug is used until if fails to give a therapeutic benefit or the patient experiences tolerability issues, upon which a new drug is given.[10] Our findings of high rates of nonadherence and discontinuation of newly initiated antipsychotic agents may be an artefact of this strategy. Though national and international guidelines for schizophrenia treatment exist, their recommendations with respect to the choice of first antipsychotic can often be vague and provide little guidance on "matching" a drug with a given patient.[30] Further, evidence pooled from clinical trials suggests that 19.8% to 66.9% of patients with schizophrenia do not achieve a full response to their antipsychotic treatment in the first 6 weeks after initiating treatment.[31] Another explanation, in addition to lack of efficacy, for the high rates of discontinuation observed shortly after treatment initiation in our sample may be adverse events associated with oral antipsychotic treatment.[5,15] Previous studies have established the frequency of treatment-related adverse events such as weight gain, extrapyramidal symptoms (EPS), anxiety, and metabolic changes among patients treated with antipsychotics.[32] Patients themselves have often identified adverse events as a key reason for poor adherence and ultimately discontinuation.[11] The potential role of adverse effects of antipsychotic treatment in non-adherence and discontinuation should be studied in the Medicare population, particularly among older and/or disabled beneficiaries who may be less capable of coping with side effects and thus more likely to discontinue. Given the known side effects of existing oral antipsychotics, our findings suggest an unmet need for new antipsychotic treatment options that are effective and tolerable to promote better treatment adherence.[33]

We identified multiple sociodemographic, clinical, and treatment-related factors associated with lower odds of adherence and higher hazard of discontinuation among Medicare beneficiaries with schizophrenia. Our study adds to the existing literature that has found younger age, female sex, and non-White race to be associated with lower odds of adherence and greater odds of discontinuation,[5] demonstrating this for the first time in the large US Medicare population. We also found that patients with evidence of previous schizophrenia-related hospitalization had lower odds of adherence and a higher hazard of discontinuation; a similar pattern was observed for patients who previously had a large number of schizophrenia-related ER visits. Finally, consistent with prior work in other patient populations,[16,34] we found that a higher antipsychotic dosing frequency was negatively associated with adherence, meaning that beneficiaries who needed to take their medication twice- or thrice-daily had lower odds of adherence compared to patients on once-daily treatment.

What actionable insights can be gleaned from these findings? First, consideration should be given to patients' age, sex, and race when choosing an initial antipsychotic treatment. Physicians should also be cognizant of patients' history of schizophrenia-related hospitalization and ER visits, as these can be indicators of previous difficulties in maintaining adherence to antipsychotic treatment. As newer antipsychotic treatments with differing mechanisms of action and better side effect profiles become available, these patients may be ideal candidates for these therapies.[33] Second, physicians should be aware of the impact that modifiable factors such as dosing frequency have on treatment success. Given widespread availability of efficacious, once-daily oral antipsychotics, there is little reason that nearly one-third of Medicare beneficiaries should be receiving twice- or thrice-daily treatment. This is particularly important for the large, vulnerable Medicare population, many of whom have multiple comorbidities and thus likely a substantial pill burden from other conditions (eg, diabetes, hypertension).

Our study has several limitations worth noting. First, as with all administrative database studies, claims data is subject to possible coding errors. Second, claims data lack detailed clinical information (eg, physician notes, patient history) that would allow for confirmation of patient experience of adverse events or physician-directed dosing frequency. Third, given the median age of our sample of 55 years, it is unlikely that many of these patients were newly diagnosed or treatment-naïve (schizophrenia onset generally occurs much earlier in life). Fourth, our sample consisted of patients initiating an oral antipsychotic treatment in the outpatient setting; patients initiating a new oral antipsychotic during an inpatient hospitalization may have had more severe disease. Fifth, although our measurement of adherence using the proportion of days covered (PDC) method has been widely used and accepted in prior studies of antipsychotic treatment,[26,27] it can only tell whether a patient filled an oral antipsychotic agent and not if they took the medication as prescribed. Additionally, claims data lack the reason for treatment discontinuation whether due to adverse events, lack of efficacy, or financial/logistical barriers. However, these limitations are offset by the advantage of having 100% Medicare claims that permits robust, nationally representative analyses. Finally, our study is generalizable only to the fee-for-service Medicare population rather than patients with other types of insurance (Medicare Advantage, Medicaid, commercial, etc). Future research should examine how Medicare Advantage enrollees compare to beneficiaries in traditional Medicare with respect to antipsychotic adherence and discontinuation. Efforts will also be needed to understand how the introduction of long-acting injectables has changed the treatment landscape for Medicare beneficiaries with schizophrenia.

Conclusion

In conclusion, this real-world study of Medicare beneficiaries with schizophrenia initiating treatment with oral antipsychotic agents found low rates of adherence and high rates of discontinuation. We identified multiple patient characteristics and modifiable factors that increase the risk for non-adherence (such as younger age, non-White race, and increased dosing frequency) and which could serve as the basis for future targeted interventions. Our findings suggest a clear unmet need for new therapeutic options that balance efficacy, convenience, and tolerability.

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CZ is an employee of Cerevel Therapeutics. JTP and SKB are full-time employees of COVIA Health Solutions, a consulting firm with clients in the biotech/pharmaceutical industry. JTP and SKB report personal fees from Cerevel Therapeutics, LLC, during the conduct of the study. The authors report no other conflicts of interest in this work.

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