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ORIGINAL RESEARCH

Impact of Early Nonadherence to Oral Antipsychotics on Clinical and Economic Outcomes Among Patients with Schizophrenia

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ABSTRACT

Introduction: To quantify early nonadherence to antipsychotic medications in patients with schizophrenia and its impact on short-term antipsychotic adherence, healthcare utilization, and costs.

Methods: Patients who initiated oral antipsychotic treatment between January 1, 2006 to September 30, 2009 were identified from the MarketScan® Commercial Claims and Encounters (CCE) database (Truven Health Analytics, Ann Arbor, Michigan, USA). Patients were required to have a diagnosis of schizophrenia determined by the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) code 295.x, be 13–65 years of age, and have ≥12 months of continuous coverage prior to and after (follow-up) the earliest antipsychotic usage (index event). Medication discontinuation was defined as a gap of 30 days in available therapy; early nonadherence was defined as having the gap 90 days from the index event. During the follow-up period, medication adherence was estimated with quarterly medication possession ratios (MPR), and all-cause and schizophrenia-related healthcare resource utilization and costs were determined.

Results: The mean time to discontinuation (TTD) was 39.5 ± 20.1 days for early nonadherence patients (n = 873) and 250.7 ± 103.3 days for patients who were adherent early (n = 589). Early nonadherence resulted in more hospitalizations (0.57 vs. 0.38; P = 0.0006) with longer length of stay (LOS, 5.0 vs. 3.0 days; P = 0.0013) and higher costs ($5,850 vs. $4,211; P = 0.0244); schizophrenia-related hospitalizations, LOS, and costs were also greater. Patients that were adherent used more

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schizophrenia-related medications (10.4 vs. 4.7; $P < 0.0001$), increasing pharmacy costs ($3,684 vs. $1,549; $P < 0.0001$). Early nonadherence was correlated with lower drug adherence at each quarter of the follow-up period.

Conclusion: Approximately 60% of patients with schizophrenia are nonadherent to antipsychotic medication early in treatment and are less likely to be adherent later. Early nonadherence resulted in more all-cause and schizophrenia-related hospitalizations with a greater LOS and cost of care.

Keywords: Early discontinuation; Hospitalization; Medical possession ratios; Medication adherence; Psychiatry; Schizophrenia

INTRODUCTION

Schizophrenia is a chronic, relapsing, mental disorder with an estimated lifetime prevalence of 0.3–0.7% and an incidence of 10.2–22.0 per 100,000 person-years [1]. It is characterized by cognitive dysfunction, motor abnormalities, negative symptoms, and positive symptoms, such as delusions and hallucinations. Schizophrenia treatment consists of a combination of pharmacological and psychosocial interventions to decrease the frequency and severity of psychotic relapses while improving the patient's functional capacity and quality of life.

The tolerability, perceived efficacy, and patient attitude toward the use of antipsychotic medication are significant factors in determining medication adherence, with poor adherence leading to treatment discontinuation [2–4]. Poor medication adherence is associated with increased symptom severity, a greater risk for violence, higher rates of substance abuse, and increased risk of relapse [5, 6]. Although it is well established that patients with schizophrenia frequently discontinue taking antipsychotic medications, often soon after treatment initiation, the impact of such early nonadherence on healthcare resource utilization is not as well understood. The objectives of this study were to determine whether early nonadherence to antipsychotic medications among patients with schizophrenia predicts later adherence to antipsychotic therapy, and to evaluate the impact of early nonadherence on healthcare utilization and its associated costs.

MATERIALS AND METHODS

Data Source

Data for the study population were extracted from the MarketScan® Commercial Claims and Encounters (CCE) database (Truven Health Analytics, Ann Arbor, Michigan, USA), which contains the inpatient, outpatient, and outpatient prescription drug experience of several million employees and their dependents (annually) located in all 10 US census regions, covered under a variety of fee-for-service and capitated health plans. The claims data include inpatient and outpatient information; fully integrated health and productivity data; laboratory data; and detailed hospital drug data, reflecting real-world treatment patterns and costs. In compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA), the database consists of fully de-identified data sets, with synthetic identifiers applied to patient-level and provider-level data to protect the identities of both the patients and data contributors.

Study Population

Patients initiating oral antipsychotic treatment between January 1, 2006 and September 30, 2009 were selected from the CCE database

based on the presence of a prescription claim for one of the following oral antipsychotic medications during the identification period: fluphenazine, paliperidone, olanzapine, risperidone, aripiprazole, clozapine, quetiapine, perphenazine, or haloperidol. The earliest prescription for an oral antipsychotic to occur during the study period was selected as the index event, with the associated medication as the index antipsychotic medication. Patients who were prescribed more than one oral antipsychotic at the index event were excluded from the study. In addition to oral antipsychotic use, patients included in the study were required to have a diagnosis of schizophrenia, be 13–65 years of age at the year of index date, and have at least 12 months of continuous medical and prescription drug coverage both prior to the index event (baseline period) and after the index event (follow-up period). The entire study period, including the baseline and follow-up period, was between January 1, 2005 and September 30, 2010. A diagnosis of schizophrenia was determined based on the presence of at least one inpatient or two outpatient physician visits on separate dates containing either a primary or secondary diagnosis of schizophrenia, identified by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code of 295.X, during the baseline period. Qualified patients were then allocated to one of two study cohorts, one consisting of patients who were nonadherent to their index antipsychotic early in treatment and the other consisting of those who were adherent. Patients were considered to have discontinued their medication if the time between two consecutive pharmacy claims for the index oral antipsychotic was 30 days greater than the days of supply of the antipsychotic medication. Time to discontinuation was defined as the period of time from the index event (initiation of oral antipsychotic therapy) to the last day of supply prior to discontinuation. Early nonadherence to antipsychotic treatment was defined as a time to discontinuation 90 days from the index event.

This article does not contain any interventional studies conducted on human or animal subjects performed by any of the authors.

Measures

Patient demographic and clinical characteristics during the baseline period were determined and compared between the early nonadherence and early adherence cohorts. Demographic variables included age at the index event, gender, geographical region of residence in the US, type of health plan coverage, and index oral antipsychotic medication. Clinical characteristics consisted of comorbid conditions identified by ICD-9-CM codes during the baseline period and Charlson Comorbidity Index (CCI) score. The CCI score is a weighted score that estimates mortality for a patient based on the occurrence of comorbid conditions and the overall disease severity, and comorbidities among patients [7]. The CCI score was calculated for each patient in the study using a macro developed by the Manitoba Centre for Health Policy, which determines the CCI based on 17 comorbid condition categories [8].

The mean time to discontinuation of the index oral antipsychotic medication was determined for each study cohort. In addition, the frequency distribution of patients who discontinued use of their index oral antipsychotic during the follow-up period, divided into 1-month intervals, was determined for the overall study population, as well as for each study cohort. Medication adherence was estimated based on the patient's medication possession ratio (MPR), which was calculated as the total number of days of drug supply during

the follow-up period divided by the total number of days in the follow-up period. The mean MPR for the follow-up period was determined for each study cohort. In addition, the MPR for each quarterly period within the follow-up period was also determined.

In order to evaluate the economic impact of early nonadherence to antipsychotic treatment, healthcare resource utilization and costs were determined and compared among study cohorts. The frequencies of inpatient, outpatient, and pharmacy utilization during the follow-up period for any reason (all-cause), as well as for schizophrenia-related treatment were evaluated. Schizophrenia-related treatment was defined as treatment with schizophrenia as either the primary or secondary diagnosis. Hospital length of stay (LOS) was determined for all-cause and schizophrenia-related hospitalizations. The associated cost for healthcare utilization per patient during the follow-up period was determined and represents the total payment from health plans, patients, and/or third party payers for the services received.

Generalized linear models were used to evaluate the association between hospitalization rates, hospital LOS, and early nonadherence while controlling for major patient demographic and clinical characteristics. The covariates included age, gender, region, CCI score, index antipsychotic medication, and other concomitant medications. As a sensitivity analysis, the generalized linear model regression analysis was also carried out among a narrower population of patients with schizophrenia identified by ICD-9-CM codes (295.0X, 295.1X, 295.2X, 295.3X, 295.5X, 295.6X, 295.8X, 295.9X).

Statistical Analyses

Descriptive statistics were used to measure and describe patient demographic and clinical characteristics, as well as all-cause and schizophrenia-related healthcare resource utilization and cost measurements at the unadjusted data level with *P*-values provided by chi-square or analysis of variance (ANOVA) tests when appropriate. Multivariate statistical analysis was used to evaluate the impact of early nonadherence versus early adherence on the number of all-cause hospitalizations and total hospital LOS by using generalized linear models with log transformation for cost data and gamma distribution as the link function, while controlling for the major patient and clinical characteristics. A *P*-value of 0.05 was used to determine the level of statistical significance. All statistical analyses were carried out using SAS 9.2 (SAS Institute, Inc., Cary, North Carolina, USA).

RESULTS

After all exclusion criteria were applied, 1,462 patients with schizophrenia were included in the overall study population. Among the study population, 873 patients (59.7%) were nonadherent to oral antipsychotic medication early with a mean time to discontinuation of 39.5 ± 20.1 days, and 589 patients were adherent to their antipsychotic medication early with a significantly longer mean time to discontinuation of 250.7 ± 103.3 days ($P < 0.0001$). Baseline patient demographics and clinical characteristics were comparable between patients who were or were not adherent to their oral antipsychotic medication early in treatment (Table 1). The most common index oral antipsychotics were risperidone, aripiprazole, quetiapine, and olanzapine. Patients within both cohorts had low comorbidity based on CCI scores (Table 2).

Of the study population, 59.7% discontinued their index antipsychotic within 90 days of initiation and only 14.2% were persistent after 12 months. Among patients with early

Table 1 Baseline patient demographics

	Early nonadherence		*P*-value
	Yes	No	
Patient count	873	589	
Age, mean (SD)	38.6 (15.6)	39.9 (15.4)	0.1127
Age group, *n* (%)			0.5081
≤17 years	66 (7.6)	38 (6.5)	
18–35 years	316 (36.2)	198 (33.6)	
36–45 years	120 (13.8)	90 (15.3)	
46–55 years	224 (25.7)	148 (25.1)	
56–65 years	147 (16.8)	115 (19.5)	
Gender, *n* (%)			0.5878
Male	435 (49.8)	302 (51.3)	
Female	438 (50.2)	287 (48.7)	
Region, *n* (%)			0.1181
Northeast	98 (11.2)	60 (10.2)	
North Central	276 (31.6)	202 (34.3)	
South	322 (36.9)	183 (31.1)	
West	171 (19.6)	139 (23.6)	
Unknown	6 (0.7)	5 (0.9)	
Health plan type, *n* (%)			0.4755
Preferred provider organization	421 (48.2)	269 (45.7)	
Health maintenance organization	180 (20.6)	145 (24.6)	
Point-of-service plan	119 (13.6)	75 (12.7)	
Point-of-service plan with capitation	2 (0.2)	2 (0.3)	
Comprehensive	105 (12.0)	77 (13.1)	
Consumer-directed health plan	19 (2.2)	11 (1.9)	
Exclusive provider organization	11 (1.3)	4 (0.7)	
Missing/unknown	16 (1.8)	6 (1.0)	
Index antipsychotic, *n* (%)			0.0005
Risperidone	246 (28.2)	191 (32.4)	
Aripiprazole	181 (20.7)	124 (21.1)	
Quetiapine	159 (18.2)	117 (19.9)	
Olanzapine	150 (17.2)	91 (15.5)	
Haloperidol	61 (7.0)	13 (2.2)	
Fluphenazine	22 (2.5)	11 (1.9)	
Paliperidone	22 (2.5)	14 (2.4)	
Clozapine	16 (1.8)	23 (3.9)	
Perphenazine	16 (1.8)	5 (0.9)	

SD standard deviation

Table 2 Comorbid conditions

	Early nonadherence		*P*-value
	Yes	No	
Patient count	873	589	
CCI score, mean (SD)	0.47 (1.02)	0.54 (1.20)	0.2272
CCI group, *n* (%)			0.3325
CCI score of 0	640 (73.3)	413 (70.1)	
CCI score of 1–2	182 (20.9)	142 (24.1)	
CCI score of 3–4	45 (5.2)	27 (4.6)	
CCI score ≥5	6 (0.7)	7 (1.2)	
Relevant comorbid conditions, *n* (%)			
Chronic pulmonary disease	95 (10.9)	80 (13.6)	0.1187
Diabetes	91 (10.4)	62 (10.5)	0.9499
Cerebrovascular disease	35 (4.0)	32 (5.4)	0.2016
Cancer	23 (2.6)	15 (2.6)	0.9175
Congestive heart failure	21 (2.4)	15 (2.6)	0.8643
Liver disease	14 (1.6)	8 (1.4)	0.7054
Peripheral vascular disease	9 (1.0)	7 (1.2)	0.7764
Dementia	9 (1.0)	12 (2.0)	0.1127
Rheumatic disease	9 (1.0)	5 (0.9)	0.7259
Renal disease	8 (0.9)	9 (1.5)	0.2846
Myocardial infarction	5 (0.6)	4 (0.7)	0.7987
Peptic ulcer disease	3 (0.3)	4 (0.7)	0.3621

CCI Charlson Comorbidity Index, *SD* standard deviation

nonadherence to their antipsychotic medication, 64.3% discontinued within 30 days of initiation, whereas 35.3% of patients who were adherent early during treatment were still using their oral antipsychotic medication for durations greater than 12 months after initiation (Fig. 1). Correspondingly, the mean MPR during the follow-up period was significantly lower among patients with schizophrenia with early nonadherence (0.22 ± 0.23 vs. 0.73 ± 0.26; $P < 0.0001$). In comparison to patients who were nonadherent early, the mean MPR in the first quarter was significantly higher for the adherent cohort in accordance with the design of the study (0.57 ± 0.29 vs. 0.99 ± 0.06, $P < 0.0001$). Of the patients who were nonadherent to their antipsychotic medication early in treatment, the mean MPR declined from 0.57 ± 0.29 during the first quarter to 0.27 ± 0.39 at the second quarter and remained low through the fourth quarter (Fig. 2). Although the MPR decreased steadily throughout the follow-up period among patients who were adherent early in treatment, patients were significantly ($P < 0.0001$) more adherent than those who were nonadherent early, with a fourth quarter MPR of 0.60 ± 0.44, which was greater than the first quarter MPR of early nonadherent patients (Fig. 2).

Early nonadherence was associated with greater healthcare resource utilization and

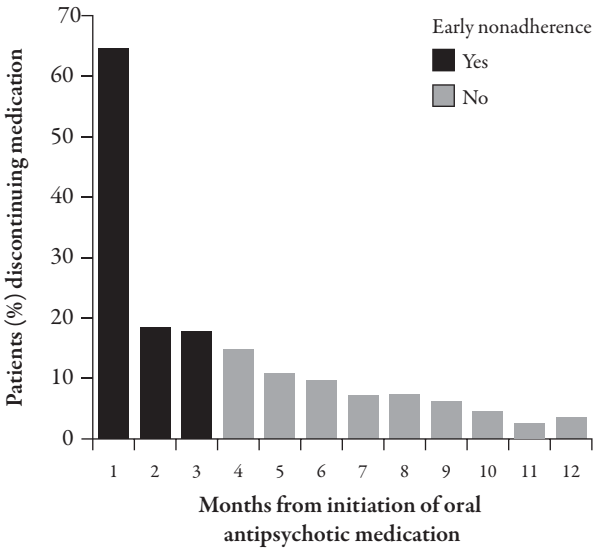

Fig. 1 Time to discontinuation. The frequency distribution of patients who discontinued antipsychotic medication at 1-month intervals during the 12-month follow-up period

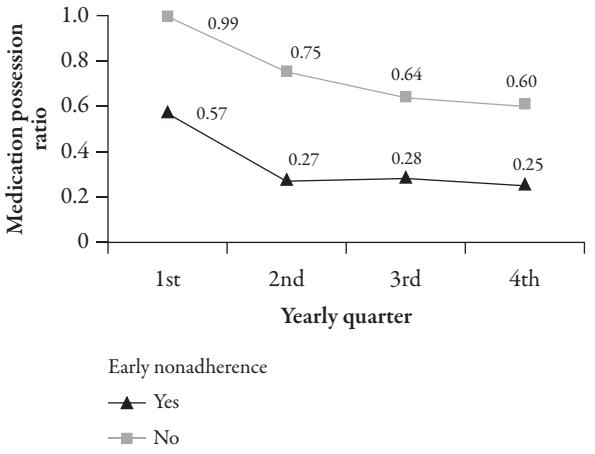

Fig. 2 Medication adherence during the follow-up period. Medication adherence was estimated by measuring medication possession ratio during each quarterly interval of the 12-month follow-up period. The overall mean medication possession ratio for patients who were nonadherent early was 0.22 ± 0.23 and 0.73 ± 0.26 for patients who were adherent early. $P < 0.0001$ at all quarters.

costs during the follow-up period (Table 3). In comparison to patients who were adherent early in treatment, patients who were nonadherent had a higher mean number of hospitalizations (0.57 vs. 0.38, $P = 0.0006$) with a longer LOS (5.0 vs. 3.0 days, $P = 0.0013$), and greater mean costs ($5,850 vs. $4,211, $P = 0.0244$). Approximately half of these hospitalizations were for schizophrenia-related care, which was also associated with a longer LOS (3.0 vs. 1.7 days, $P = 0.0136$) and greater costs ($2,952 vs. $1,969, $P = 0.0465$) than that of patients who were adherent early in treatment. Outpatient care, for any cause as well as for schizophrenia-related care, did not significantly differ among study cohorts. The number of pharmacy claims and associated costs were greater for patients who were adherent early in treatment. Schizophrenia-related medications accounted for 16% and 25% of the pharmacy claims among patients with and without early nonadherence, respectively. Although total costs for all-cause resource utilization was comparable among study cohorts, the increased cost of schizophrenia-related medications among patients who were adherent early in treatment resulted in greater total costs for schizophrenia-related resource utilization ($6,660 vs. $5,358, $P = 0.0211$).

After adjusting for patient differences, early nonadherence was associated with an estimated increase in the number of hospitalizations per year of 0.33 (95% confidence interval [CI] 0.11–0.54) and a longer hospital LOS of 0.38 days (95% CI 0.02–0.73; Table 4). A sensitivity analysis was carried out among an alternative schizophrenia population in which a narrower range of ICD-9-CM codes was used to identify patients with schizophrenia (Table 4). In the sensitivity analysis, the impact of early nonadherence on the number of hospitalizations was similar to that observed for the overall study population in terms of direction and statistical significance. The impact of early nonadherence on hospital LOS was also similar to that observed for the overall

Table 3 Resource utilization and costs during the follow-up period

	Early nonadherence		*P*-value
	Yes	No	
All-cause resource utilization			
Hospitalizations, mean (SD)			
Number of hospitalizations	0.57 (1.08)	0.38 (0.90)	0.0006
Total LOS (days)	5.0 (13.6)	3.0 (8.6)	0.0013
Total payment	$5,850 (14,554)	$4,211 (12,169)	0.0244
Outpatient claims, mean (SD)			
Number of claims	49.8 (54.3)	49.7 (49.0)	0.9621
Total payment	$5,773 (8,678)	$5,882 (9,672)	0.8216
All Rx claims, mean (SD)			
Number of claims	29.3 (28.5)	41.5 (32.0)	<0.0001
Total payment	$3,777 (6,503)	$7,543 (26,562)	<0.0001
Total payment, mean (SD)	$15,400 (22,149)	$17,636 (33,791)	0.1265
Schizophrenia-related resource utilization			
Hospitalizations, mean (SD)			
Number of hospitalizations	0.29 (0.70)	0.16 (0.52)	0.0003
Total LOS (days)	3.0 (11.2)	1.7 (7.1)	0.0136
Total payment	$2,952 (10,189)	$1,969 (7,658)	0.0465
Outpatient claims, mean (SD)			
Number of claims	7.7 (13.7)	9.1 (13.7)	0.0589
Total payment	$858 (2,478)	$1,008 (2,531)	0.2606
All Rx claims, mean (SD)			
Number of claims	4.7 (5.2)	10.4 (6.3)	<0.0001
Total payment	$1,549 (2,065)	$3,684 (2,985)	<0.0001
Total payment, mean (SD)	$5,358 (11,360)	$6,660 (9,295)	0.0211

LOS length of stay, *Rx* prescription, *SD* standard deviation

study population, but it was not statistically significant due to the smaller patient sample (early nonadherence: yes: $n = 495$; no: $n = 320$).

DISCUSSION

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial reported that 74% of the patients discontinued treatment within the 18-month study period, with a median time to discontinuation of 4.6 months [9]. Time to all-cause medication discontinuation has been recognized as an important global index of antipsychotic medication effectiveness, safety, and tolerability [9]. Although some studies have evaluated the impacts of nonadherence and partial adherence on relapse rate and healthcare utilization, there is little information in the published literature on whether greater degrees of nonadherence are associated with worse schizophrenia patient outcome and, consequently, greater healthcare resource utilization.

Table 4 Multivariate regression results for evaluation of impact of early nonadherence versus early adherence on hospital resource utilization for any cause

Hospital resource utilization	Difference[a]	CI lower	CI upper	*P*-value
Overall study population				
Hospitalization count	0.33	0.11	0.54	0.0027
Length of stay (days)	0.38	0.02	0.73	0.0371
Sensitivity study population[b]				
Hospitalization count	0.35	0.07	0.62	0.0155
Length of stay (days)	0.42	−0.08	0.91	0.0982

P-values were calculated using a generalized linear model
CI 95% confidence interval, *Lower* lower bound, *Upper* upper bound
[a] Positive value indicates that resource is higher among early nonadherence cohort
[b] Sample size (early nonadherence: yes: $n = 495$; no: $n = 320$)

In the current study, approximately 60% of patients were nonadherent to their antipsychotic medication early on in treatment and, in comparison to those who did not discontinue antipsychotic medication early, they were much less likely to adhere to therapy over the course of the following 9 months. Moreover, nearly two-thirds of patients who were nonadherent early discontinued treatment within the first month after initiation of antipsychotic medication. Nonadherence to antipsychotic medication early after initiation was associated with significantly increased all-cause hospitalizations and schizophrenia-related hospitalizations with greater LOS, resulting in significantly greater costs for inpatient care. Antipsychotic prescription claims, as expected, were higher for the more adherent cohort and the associated cost was 2.4-fold greater than that for patients who were nonadherent early.

The cost for antipsychotic medication is one possible deterrent for their continued use, although as this study was a database claims analysis, the authors were unable to determine the reasons why patients were nonadherent early. Liu-Seifert et al. reported in 2005 that among clinical trial patients with schizophrenia or a related disorder, poor psychiatric response along with worsening symptoms was the predominant cause of patients discontinuing treatment [10]. The study of Liu-Seifert et al. in 2005 also found that early response to treatment was associated with a greater likelihood of maintaining antipsychotic therapy [10]. The results of the present study corroborate others that have demonstrated that once patients discontinue antipsychotic therapy they have a low likelihood of resuming treatment [11, 12]. The results of these studies and the present study imply that management of schizophrenia may improve if the problem of nonadherence is addressed by interventions that are timed at the onset of antipsychotic initiation [11, 12]. A potential strategy to improve adherence early on in antipsychotic therapy and likely effectiveness may be to measure serum medication concentrations to obtain not only an objective estimate of adherence/effectiveness, but also provide an opportunity to build insight into treatment [13, 14].

Poor adherence and discontinuation of antipsychotic medication has been associated with

an increased risk of relapse, a greater likelihood of an episodic course, and increased hospitalization with higher costs [15–18]. One study comparing different degrees of nonadherence has reported that as the severity of nonadherence increases there is an increased risk for the return of psychotic symptoms (hazard ratios 3.7–28.5) in the early course of schizophrenia [19]. Also, discontinuation of antipsychotic medication for as little as 1–10 days has been found to nearly double the risk of hospitalization, with a gap of over 30 days resulting in an approximately fourfold increased risk of hospitalization [20, 21]. Relapse, in turn, negatively influences adherence to antipsychotic medication, creating a cycle of recurrent schizophrenia exacerbation leading to poor long-term patient outcome [22]. Observational studies have reported that use of long-acting injectable formulations of antipsychotic medications, particularly second-generation antipsychotics, abates the debilitating cycle of nonadherence and relapse for patients with schizophrenia [23–25]. Additionally, reviews of clinical trials and observational studies have concluded that administration of a long-acting injectable antipsychotic is a good alternative to oral antipsychotic therapy for patients with schizophrenia early on in the course of the disease [22, 26].

Limitations

The current study evaluated healthcare resource utilization and costs among a commercially insured study population using a claims database and did not take into account the indirect costs resulting from schizophrenia-related absences. Additionally, using pharmaceutical claims contained within the MarketScan database, the authors estimated medication adherence for patients within the study cohorts by calculating MPRs, which has some drawbacks, as do all current measurements of medication adherence. MPRs provide objective information on the collected prescription, dosage, and supply, but no information regarding a patient's daily usage/adherence of medication. Therefore, patients who discontinued oral antipsychotic treatment for the remainder of the follow-up period could not be differentiated from those who resumed treatment after a 30-day gap. In this study, the authors only evaluated adherence to the index oral antipsychotic and did not take into account that some patients may have switched to another antipsychotic drug. Thus, the study cohorts were heterogeneous in these regards, which may allow for broader generalizability to patients with schizophrenia initiating oral antipsychotic medications in naturalistic settings. By study design, patients who were nonadherent early discontinued their index antipsychotic medication during the first 90 days and, thus, the MPRs of early nonadherent patients were lower than those of patients within the early adherent cohort.

The MarketScan database consists of claims submitted by healthcare providers to insurance companies for reimbursement on behalf of individuals employed by various companies and such claims are subject to possible coding errors, coding for the purpose of rule-out rather than actual disease, and undercoding, either by the healthcare provider or due to limitations imposed by the database. It is also difficult to obtain complete medical histories based on claims data. Changes in insurance coverage can limit the amount of continuous data available and, consequently, constrain the study sample sizes available for analysis. The MarketScan CCE database is based on a large convenience sample and, therefore, is not random, and it may contain biases or fail to generalize well to other populations, particularly those who have alternate healthcare coverage,

such as those provided by the government (Medicare, Medicaid). In addition, patient demographics and clinical characteristics recorded in the database may not correspond to the overall US population.

In conclusion, the results of this study emphasize that to improve the treatment of patients with schizophrenia it is critical to develop strategies that assist them in adherence to antipsychotic drug therapy at treatment onset, as early nonadherence is a predictor of poor later drug adherence and greater requirement for costly inpatient care.

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Conflict of interest. Dr. Offord is an employee of Otsuka America Pharmaceutical, Inc. Dr. Mirski is an employee of Otsuka America Pharmaceutical, Inc. Dr. Lin is an employee of Novosys Health, which has received financial funds from Otsuka America Pharmaceutical, Inc., in connection with conduction of this study and development of this manuscript. Dr. Wong is a paid consultant for Otsuka America Pharmaceutical, Inc., in connection with conducting this study and development of this manuscript.

Compliance with Ethics Guidelines. This article does not contain any interventional studies with human or animal subjects performed by any of the authors.

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