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Choice of Atypical Antipsychotic Therapy for Patients with Schizophrenia: An Analysis of a Medicaid Population

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ABSTRACT

Background: In patients treated at Veterans Affairs facilities, demographic and clinical characteristics have been found to influence the choice of atypical antipsychotic drugs. However, little is known about the influences on the choice between olanzapine and risperidone in patients with schizophrenia enrolled in Medicaid.

Objective: The aim of this study was to determine whether demographic and/or clinical characteristics and/or medical-service utilization before treatment were related to the choice of olanzapine versus risperidone therapy using data from a Medicaid population with schizophrenia.

Methods: The study sample was identified in the North Carolina (NC) Medicaid claims database. Data were included from patients aged 18 to 64 years who were diagnosed with schizophrenia; had initiated treatment with olanzapine or risperidone between July 1, 1998, and October 31, 2000; had not used atypical antipsychotics during the 6 months before the start of treatment; and were continuously eligible in the NC Medicaid program during the 6 months before the start of treatment. Multivariate logistic regression models were used to estimate the likelihood of the choice of olanzapine or risperidone associated with patients' demographic and clinical characteristics and medical-service utilization during the 6 months before the initiation of treatment.

Results: A total of 764 patients (383 women, 381 men; mean age, 42.1 years) were included in the analysis: 420 were initially prescribed olanzapine and 344 were prescribed risperidone. Men were more likely than women to be prescribed olanzapine compared with risperidone. Patients who had a hospitalization related to a psychiatric condition during the pretreatment period were more likely to be prescribed olanzapine compared with risperidone (OR = 1.530; P = 0.043). Significant regional variation in the likelihood of prescribing olanzapine or risperidone was found, with patients being prescribed risperidone at

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a higher rate compared with olanzapine in 2 counties with the largest schizophrenic populations.

Conclusions: In this study of data from patients with schizophrenia identified in the NC Medicaid claims database, sex, a history of psychiatric-related hospitalization, and geographic residence were found to be correlated with the selection of treatment with olanzapine versus risperidone. These findings need to be confirmed in large, randomized, prospective studies. (*Curr Ther Res Clin Exp.* 2005;66:463–474)

Key words: atypical antipsychotics, olanzapine, risperidone, schizophrenia, NC Medicaid.

INTRODUCTION

The introduction of atypical antipsychotics, including olanzapine, risperidone, clozapine, and quetiapine, during the 1990s greatly advanced pharmacologic care for patients with schizophrenia. However, atypical antipsychotics cost considerably more than typical antipsychotics (eg, haloperidol, chlorpromazine) and, facing increasing budget pressures, third-party payers are demanding a better understanding of the cost-effectiveness of competing drug regimens. To this end, numerous pharmacoeconomic studies have been conducted to compare the economic outcomes of atypical and typical antipsychotics.[1–13] Recently, attention has turned to comparative assessments of the treatment outcomes of atypical drugs, with particular focus on the 2 most frequently prescribed atypical antipsychotics—olanzapine and risperidone.[14–22]

Previous studies have focused primarily on posttreatment cost comparisons based on retrospective data, mostly claims data.[23] However, despite the importance of assessing posttreatment outcomes, it is crucial that groups of patients sampled from claims databases are comparable. Thus, an important part of any retrospective assessment is to assess how and why the patients using a particular drug might differ in demographic and clinical characteristics and pretreatment resource utilization. Such information would enable researchers to design a treatment model that could control for incomparable characteristics while comparing treatment outcomes of olanzapine and risperidone.

Although olanzapine and risperidone are in the same therapeutic category, they have different chemical properties and exhibit different adverse-effect profiles, which might influence treatment choice. For example, olanzapine treatment is associated with more weight gain compared with risperidone, which may influence clinicians' prescribing decisions.[24,25] In addition, as evidenced in the literature,[15,16] the effect of "time to market" might also play an important role in clinicians' prescribing behavior. For example, a relatively new drug might be more likely to be prescribed for severely ill and/or treatment-resistant patients compared with older medications in the same class.[15,16]

Some evidence has shown that demographic and clinical characteristics of patients also might influence the choice of an atypical antipsychotic agent.

Using data from the national Veterans Affairs (VA) administrative databases, Leslie and Rosenheck[26] found that the disabled, older, and black patients were less likely to use an atypical antipsychotic compared with other patients; but those with comorbid psychiatric disorders or who had used inpatient psychiatric services in the previous year were more likely to receive atypical antipsychotics. Using a signal-detection approach based on pharmacy records of the VA Palo Alto Health Care System, Yesavage et al[27] found that patients' age and disease severity were associated with the choice of atypical antipsychotics. Specifically, patients aged <55 years and who had more inpatient treatment days during the previous year were more likely to be prescribed olanzapine compared with risperidone. These findings were corroborated by Ren et al,[28] who, using the VA Health Administrative database, found that age, race, and marital status and some clinical characteristics were correlated with the choice between olanzapine and risperidone.

Because most schizophrenic patients are enrolled in state Medicaid programs, decision-makers and clinicians are particularly interested in the factors that might be associated with variations in the selection of atypical antipsychotics in these patients. Thus, the aim of this study was to determine whether patients' demographic and/or clinical characteristics and/or medical-service utilization 6 months before treatment was/were related to the choice of olanzapine versus risperidone therapy in a Medicaid population with schizophrenia.

MATERIALS AND METHODS

Data Source

The study sample was drawn from the North Carolina (NC) Medicaid claims database,[29] which included files concerning Medicaid eligibility, prescription-drug claims, and medical-service claims. The eligibility file included patients' demographic characteristics (age, sex, race, and county of residence) and a history of Medicaid eligibility. The prescription-drug claims file included National Drug Codes[30] for prescribed drugs, the number of days each drug was supplied, and the dates on which each drug was dispensed. Medical-service claims documented detailed utilization information for each clinical procedure performed, the date of service of each procedure, expenditure, and diagnosis. We aggregated medical services into 4 categories: *hospitalization, emergency care, outpatient visits,* and *long-term care facility visits.* A unique scrambled patient identifier was used as a key to link and merge the 3 files for data analysis. Access to patient data was provided by the NC State Medicaid Agency. We were fully compliant with Health Insurance Portability and Accountability Act regulations,[31] and institutional review board approval was not required.

Study Design and Selection Criteria

Data from patients enrolled in the NC Medicaid program were included in this study if the patients had ≥1 medical-service claim containing a diagnosis of

schizophrenia (identified by the *International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*][32] code 295.xx); were aged 18 to 64 years as of July 1, 1998; initiated treatment with olanzapine or risperidone between July 1, 1998, and October 31, 2000; had not used an atypical antipsychotic drug during the 6 months before the start of treatment; and were continuously enrolled in the NC Medicaid program during the 6 months before the initiation of treatment. At least 2 claims for atypical antipsychotic drugs were required after the index date to eliminate trial use of these drugs.

We selected olanzapine and risperidone for study for 3 reasons. First, although other atypical antipsychotics, including clozapine and quetiapine, were also available during the study period, only a small number of patients in the NC Medicaid database used clozapine or quetiapine. Second, olanzapine and risperidone have similar profiles in terms of efficacy, timing of commercial availability, and use in the schizophrenic population. Third, both olanzapine and risperidone were preferred drugs in the formulary in the NC Medicaid program.

Patients were assigned to treatment cohorts based on the drug first received. The date of the initial prescription for each study drug was designated as the *index date*.

Medical-service utilization was categorized based on the principal diagnosis, as follows: *schizophrenia conditions* (*ICD-9-CM* code 295.xx); *mental-health conditions*, including major diseases (eg, bipolar disorder, major depressive disorder; *ICD-9* codes 290–319); and *all health conditions* (any *ICD-9* code).

Statistical Analysis

Demographic and clinical characteristics for patient cohorts were described using percentiles. The Student *t* test was used to assess differences in continuous variables between treatment cohorts. The χ^2 test was used to compare categoric variables associated with the groups of patients.

To estimate the correlation of treatment choice with patient demographic and clinical characteristics and medical services utilization during the 6-month pretreatment period, multivariate logistic regression analyses were run for 3 treatment choice models. The models included the same set of patient demographic characteristics, type of schizophrenia, and comorbidities, but were differentiated by the use of medical services due to different conditions. Specifically, in models 1 to 3, the dummy variable of *medical services utilization* specified whether utilization was for mental-health conditions, schizophrenia conditions, or all health conditions, respectively. Because direct measures of severity of illness were not present in the database, a set of explanatory variables (ie, type of schizophrenia; whether patients used emergency department, in-patient hospital and/or long-term care facility services; and whether patients had been treated with depot antipsychotics), were used as proxies for disease severity. All statistical analyses were performed using SAS version 8.2 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Descriptive Statistics

A total of 7869 patients in the NC Medicaid database had a diagnosis of schizophrenia. Of these, 764 patients (383 women, 381 men; mean age, 42.1 years) met the inclusion criteria and were included in the present analysis. Of these, 420 (55.0%) and 344 (45.0%) patients were included in the olanzapine and risperidone cohorts, respectively. The demographic and clinical characteristics of the 2 cohorts are presented in **Table I**. The only statistically significant difference between the 2 cohorts was sex: the olanzapine cohort included significantly more men compared with the risperidone cohort (228 [54.3%] vs 153 [44.5%]; $P = 0.007$). We observed some geographic variation across counties; risperidone was prescribed at a significantly higher rate compared with olanzapine in 2 counties with the largest schizophrenic populations—Mecklenburg (7.3% vs 3.6%; $P < 0.023$) and Guilford (5.5% vs 2.4%; $P < 0.024$). Rates of medical-service utilization were statistically similar in the intent-to-treat populations of the 2 treatment cohorts.

Logistic Regression Analysis

Table II shows the results of the 3 treatment-choice models used in the multivariate logistic regression analyses. After the set of observed confounding factors were controlled for, all 3 models showed that the likelihood of selecting olanzapine versus risperidone was correlated with a set of patient factors—sex, county of residence, and whether a patient was hospitalized for a psychiatric condition. Men were more likely than women to receive olanzapine compared with risperidone. This finding was true for all 3 models, with ORs of 1.443 ($P = 0.025$) in model 1, 1.441 ($P < 0.027$) in model 2, and 1.384 ($P = 0.048$) in model 3. Second, the finding that risperidone was prescribed at significantly higher rates in Mecklenburg and Guilford counties was also true across all 3 models (ORs: model 1, 0.442 [$P < 0.021$] and 0.405 [$P < 0.027$], respectively; model 2, 0.460 [$P < 0.028$] and 0.399 [$P < 0.025$], respectively; and model 3, 0.451 [$P < 0.023$] and 0.376 [$P < 0.019$], respectively).

In terms of medical-service utilization, model 1 showed that patients who had had any hospitalizations related to a psychiatric condition were more likely to begin treatment with olanzapine compared with patients without such an event (OR, 1.530 [$P = 0.043$]). In contrast, models 2 and 3 showed no such correlation. In addition, no statistical correlations were found between treatment choice and any of the other variables analyzed (age, race, type of schizophrenia, and number of comorbidities).

DISCUSSION

Using multivariate logistic models, we examined the association between the selection of atypical antipsychotic drugs and patients' demographic and clinical characteristics, comorbidities, and pretreatment resource utilization. Our

Table I. Baseline demographic and clinical characteristics of the study patients.*

Characteristic	Olanzapine (n = 420)	Risperidone (n = 344)	*P*
Age			
Mean (SD), y	41.4 (11.1)	42.9 (10.8)	<0.057
Group, no. (%)			
18 to <35 y	116 (27.6)	79 (23.0)	<0.143
35 to <43 y	106 (25.2)	95 (27.6)	<0.459
43 to <52 y	112 (26.7)	85 (24.7)	0.539
52 to <65 y	86 (20.5)	85 (24.7)	<0.163
Sex, no. (%)			
Male	228 (54.3)	153 (44.5)	0.007
Female	192 (45.7)	191 (55.5)	<0.015
Race, no. (%)			
White	196 (46.7)	145 (42.2)	<0.212
Black	179 (42.6)	162 (47.1)	<0.216
Other	45 (10.7)	37 (10.8)	<0.986
County of residence, no. (%)†			
Gaston	25 (6.0)	14 (4.1)	<0.240
Wake	21 (5.0)	23 (6.7)	<0.320
Cumberland	16 (3.8)	15 (4.4)	0.701
Mecklenburg	15 (3.6)	25 (7.3)	<0.023
Guilford	10 (2.4)	19 (5.5)	<0.024
Other	333 (79.3)	248 (72.1)	<0.021
Type of schizophrenia, no. (%)‡			
Undifferentiated	161 (38.3)	120 (34.9)	<0.326
Paranoid	142 (33.8)	128 (37.2)	<0.329
Schizoaffective	138 (32.9)	112 (32.6)	<0.931
Other	127 (30.2)	95 (27.6)	<0.572
No. of comorbidities, mean (SD)	3.5 (2.4)	3.7 (2.4)	<0.261

*Percentages may not total 100% due to rounding.
†These 5 counties had the largest schizophrenia populations.
‡Some patients received >1 diagnosis.

study yielded several findings. An association was found between the choice of atypical drug treatment for schizophrenic patients and health care utilization. In particular, patients who had a psychiatric-related hospitalization were more likely to be given olanzapine than risperidone therapy.

Although the 2 treatment groups were found to have different rates of hospitalization for psychiatric conditions, they showed no difference in rates of hos-

Table II. Results from multivariate logistic models (dependent variable = choice of olanzapine vs risperidone).

	Model 1*			Model 2†			Model 3‡		
Variable	*r*	OR	*P*	*r*	OR	*P*	*r*	OR	*P*
Age group									
35 to <43 y	−0.2434	0.784	<0.253	−0.2709	0.763	<0.202	−0.2616	0.770	<0.219
43 to <52 y	−0.0400	1.041	<0.855	0.0011	1.001	<0.997	−0.0078	0.992	<0.972
52 to <65 y	−0.2261	0.798	<0.335	−0.2524	0.777	<0.283	−0.3208	0.726	0.184
Male sex	0.3666	1.443 (95% CI, 1.047–1.988)	0.025	0.3654	1.441 (95% CI, 1.045–1.988)	<0.027	0.3251	1.384 (95% CI, 1.003–1.911)	0.048
Race									
Black	−0.1360	0.873	<0.415	−0.1287	0.879	<0.439	−0.1027	0.902	<0.540
Other	0.0564	1.058	<0.829	0.0550	1.057	<0.833	0.0841	1.088	<0.747
County of residence									
Wake	−0.3620	0.696	<0.263	−0.4142	0.661	<0.201	−0.3451	0.708	<0.289
Mecklenburg	−0.8158	0.442 (95% CI, 0.221–0.883)	<0.021	−0.7771	0.460 (95% CI, 0.230–0.918)	<0.028	−0.7963	0.451 (95% CI, 0.228–0.894)	<0.023
Guilford	−0.9041	0.405 (95% CI, 0.182–0.901)	<0.027	−0.9191	0.399 (95% CI, 0.179–0.888)	<0.025	−0.9777	0.376 (95% CI, 0.167–0.846)	<0.019
Gaston	0.4694	1.599	<0.200	0.5341	1.706	<0.144	0.5419	1.719	<0.140
Cumberland	−0.1621	0.850	<0.673	−0.2915	0.747	<0.444	−0.3230	0.724	<0.405
Type of schizophrenia									
Paranoid	−0.2161	0.806	<0.219	−0.0864	0.917	0.663	−0.2107	0.810	<0.218
Schizoaffective	0.0257	1.026	<0.888	0.1461	1.157	<0.456	0.0308	1.031	<0.861
Undifferentiated	0.1778	1.195	<0.296	0.2474	1.281	<0.177	0.1497	1.162	<0.373
Other	0.0425	1.043	<0.846	0.1242	1.132	<0.579	0.0606	1.063	<0.779

(continued)

Table II. (Continued)

Variable	Model 1*			Model 2†			Model 3‡		
	r	OR	*P*	*r*	OR	*P*	*r*	OR	*P*
Comorbidities	–0.0260	0.974	<0.449	–0.0251	0.975	<0.465	–0.0182	0.982	<0.646
Utilizations									
Depot	0.2438	1.276	<0.237	0.1975	1.218	<0.335	0.1994	1.221	<0.332
ED	–0.2666	0.766	<0.347	0.0246	1.025	<0.946	–0.1319	0.876	0.474
Outpatient	–0.3515	0.704	<0.310	–0.2538	0.776	<0.282	–1.5339	0.216	<0.175
Inpatient	0.4253	1.530 (95% CI, 1.013–2.310)	0.043	–0.0394	0.961	<0.869	0.1991	1.220	<0.300
LTCF	0.2442	1.277	<0.816	–0.5650	0.568	<0.660	0.2141	1.239	<0.263

ED = emergency department; LTCF = long-term care facility.
*Medical-service utilization was psychiatric related.
†Medical-service utilization was schizophrenia related.
‡Medical-service utilization was all-health related.

pitalization for schizophrenia as a primary admitting diagnosis or for all other conditions. Among others, a compelling explanation for this pattern can be offered by the way our study sample was drawn. In deriving the study sample, one of the inclusion criteria was that patients must not have used any atypical antipsychotic drug during the 6 months before the study. Most patients did not, in fact, have a claim for a schizophrenia-related visit. On the other hand, they had been treated for other psychiatric illnesses. As a result, their utilization of health care, including hospitalization, would be recorded as services for psychiatric conditions or all other disease conditions.

We also found that olanzapine and risperidone were prescribed for men and women at different rates. The ORs for prescribing olanzapine for men were 1.443, 1.441, and 1.384 in models 1, 2, and 3, respectively, suggesting male patients were more likely to receive olanzapine. Previous studies reported significant gender differences in the use of olanzapine versus risperidone,[28,33] but their results were not adjusted for other factors and might not reflect the true magnitude of this association with the gender. The gender difference could be explained by the differences in symptom presentation and sensitivity to weight gain between men and women.[25]

Finally, we found regional variation in prescribing patterns for olanzapine versus risperidone. We observed that in 2 of the counties with the largest schizophrenic populations, risperidone was prescribed at a significantly higher rate compared with olanzapine. Factors such as urban versus rural differences in patients' symptoms or physicians' practices could play a role in the choice of antipsychotic medication across counties. Regional variation in prescribing the 2 atypical drugs was found in a previous study using a Texas Medicaid population.[16] In that study, several factors were proposed to explain the regional differences, including industry marketing practices, opinion leaders, and managed care policies. A regional difference in physicians' prescribing practices was suggested as an important covariate in the prescription of olanzapine versus haloperidol.[33] Regional variations in prescribing and in general medical practices in treating other disease states have been noted for some time.[34] Variations in use for a number of medical and surgical procedures have been a source of interest for health policy makers and insurers concerned about cost and outcomes. Classic studies include the observation of widely disparate rates for common surgical procedures, such as tonsillectomies, hysterectomies, and cholecystectomies, in different communities.[34] Citrome et al[35] also found variation in depot antipsychotic utilization rates.

Using the NC Medicaid patient population, our study suggests the existence of sample selection bias in the prescribing of atypical antipsychotics, evidenced by the fact that disease states in 1 group were different from those in the other group. We found differences in sex, geographic region, and disease severity when olanzapine and risperidone were prescribed to patients with schizophrenia.

Given that current practice offers more options than the 2 treatments assessed in the present study, our study had several limitations. Because this study was based on NC Medicaid claims databases, caution must be used in

extrapolating the results to other populations or disease states. In addition, our sample size was relatively small, particularly for the risperidone cohort. It is also worth noting that the ORs were not particularly high. Some epidemiologists view ORs <2 as possibly being attributable to undetected confounding variables, ORs between 2 and 3 as more likely to be accurate, and ORs >3 as substantial. Our findings were also limited by the time period and completeness of the data set available to us. We might not have included other potentially important explanatory variables. For example, we did not have data on characteristics of the prescribing physicians or measures of symptoms or symptom severity. In general, pharmacoepidemiologic studies using claims databases are not inherently designed to answer important research questions and are associated with challenges in addressing all potential confounders. Methods such as the use of propensity scores and instrumental variables can be used in combination with appropriate multivariate regression models to ensure equivalence of groups when conducting claims database studies of the association between drug exposure, economic costs, and health outcomes. A prospective, randomized study design would be an effective way to answer these questions. Nonetheless, the results of this study serve as a good starting point to think more critically about selection bias problems in further nonrandomized studies that involve a larger and possibly more general population, ideally with national representation, and that include other factors that could influence prescribing practices.

The findings of the present study underscore the importance of controlling for sample selection bias in retrospective studies comparing the treatment effects of alternative drug regimens on cost and health outcomes. The association reported in this study is interesting, but the study design and low ORs limit the ability to consider this association as a true cause-and-effect relationship.

CONCLUSIONS

In this study of data from patients with schizophrenia identified in the NC Medicaid claims database, sex, a history of psychiatric-related hospitalization, and geographic residence were correlated with the selection of treatment with olanzapine versus risperidone. These findings need to be confirmed in large, randomized, prospective studies.

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