Abstract - 25964

Objective: Examine the effect of atypical antipsychotic half-life on the risk of psychiatric hospital admission and emergency room visits among adults diagnosed with schizophrenia.

Method: Retrospective longitudinal claims-based cohort study of adult Medicaid beneficiaries with schizophrenia who were prescribed antipsychotic monotherapy following hospital discharge between 1/1/04 and 12/31/06. Cox proportional hazards models compared adjusted hazards of psychiatric hospital admission among patients treated with oral antipsychotics that have either a long [risperidone ($t_{1/2}$=20 hours), olanzapine ($t_{1/2}$=30 hours), aripiprazole ($t_{1/2}$=75 hours)] (n=1,479) or short [quetiapine ($t_{1/2}$=6 hours), ziprasidone ($t_{1/2}$=7 hours)] (n=837) half-life. Day level models controlled for baseline background characteristics and antipsychotic adherence over time as measured by gaps in the prescription record. Similar analyses examined either psychiatric hospitalization or emergency room visit as an endpoint.

Results: The unadjusted rate of psychiatric hospitalization was significantly lower for long (0.38/patient-year) versus short (0.52/patient-year) half-life antipsychotics (p<.001). A significantly lower rate of hospitalization/emergency visits was also evident for long (0.74/patient-year) versus short (1.06/ patient-year) half-life antipsychotics (p<.001). As compared with short half-life antipsychotic drugs, the adjusted hazard ratio associated with long half-life medications was 0.80 (95% CI: 0.67-0.96) for psychiatric hospitalization and 0.77 (95% CI 0.67-0.88) for combined hospitalization/emergency visits. The corresponding number needed to treat with long, rather than short, half-life medications to avoid 1 hospitalization was 16 patients for 1 year and to avoid 1 hospitalization or emergency visit was 11 patients for 1 year.

Conclusions: In the management of schizophrenia, longer acting atypical antipsychotics were associated with a lower risk of psychiatric hospital admission.

Sensitivity of Atypical Antipsychotics to Partial Adherence: Analysis of a Medicaid Population

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Introduction

Despite the existence of multiple pharmacologic treatments and the introduction of newer, second-generation antipsychotics (SGAs), schizophrenia remains a complex and difficult-to-treat condition.

In general, schizophrenia patients who discontinue antipsychotics are twice as likely to be rehospitalized as those who take them appropriately.[1]

Pharmacologic differences among the SGAs may make the strength of the link between adherence and outcomes different for different drugs. Specifically, SGAs with longer half-lives may be less susceptible to the impact of imperfect adherence.

We hypothesized that, for a given level of adherence, hospitalizations would be less frequent among users of long half-life SGAs.

Objectives

Primary Objective: To determine whether schizophrenia patients receiving SGAs with long half-lives (i.e., risperidone, olanzapine, and aripiprazole, which require only once-daily dosing) were less likely than those receiving short half-life SGAs (i.e., quetiapine and ziprasidone, which require twice-daily dosing) to be rehospitalized when they were not adherent to their medications.

Secondary Objective: To determine whether there were fewer hospitalizations among patients using SGAs with long half-lives than among users of SGAs with short half-lives, after controlling for baseline differences.

Study Design and Methods

A retrospective cohort study using MedStat's MarketScan Medicaid database, a Health Insurance Portability and Accountability Act (HIPAA)-compliant administrative claims dataset, which aggregates Medicaid data from multiple states.

Inclusion Criteria:

Age 18-64 years

Between 1/1/2004 and 12/31/2006, had at least 1 medical claim for an inpatient hospitalization with schizophrenia (ICD-9-CM 295) as the primary diagnosis, or another mental disorder (ICD-9-CM 290-294, 296-319) as the primary diagnosis and schizophrenia as a secondary diagnosis

Discharged on SGA monotherapy and filled at least two prescriptions in the 90 days after discharge

Exclusion Criteria:

Had any medical claims for an inpatient hospitalization with a mental disorder (ICD-9-CM 290-319) as the primary diagnosis during the 6 months before the baseline hospitalization

Not continuously enrolled for at least 6 months before the index date

Table 1. Half-Lives of Atypical Antipsychotics

Atypical Antipsychotic	Half-life (Hours)	Dosing Schedule
Quetiapine	6	Twice daily
Ziprasidone	7	Twice daily
Risperidone[a]	20	Once daily
Olanzapine	30	Once daily
Aripiprazole	75	Once daily

[a] not including risperidone long-acting injection

Short half-life cohort – included patients using drugs requiring twice-daily dosing (quetiapine and ziprasidone)[2,3]

Long half-life cohort – included patients using drugs requiring once-daily dosing (aripiprazole, olanzapine, and risperidone)[4-6]

If there were multiple admissions, the first qualifying one was used as the baseline hospitalization

Index date - The date of the second fill after baseline hospitalization.

Patients were followed until the first of four events occurred: 1) fill of a prescription for a second SGA, 2) discontinuation of the index medication (refill gap >30 days), 3) the end of enrollment, or 4) the end of the study (12/31/2007).

Primary outcome – Hospitalizations and/or emergency department (ED) visits for mental disorder(s).

Secondary outcome - Hospitalizations and/or ED visits for schizophrenia.

Other study variables - patient demographics, length of stay (LOS) for the baseline hospitalization, selected mental disorder comorbidities, number of chronic conditions, other medication used for mental disorders, and health service use.

Because schizophrenia may lead to hospitalization with a primary diagnosis of another mental condition, we chose care for any mental disorder, rather than schizophrenia alone, as the primary outcome.

STATISTICAL METHODS

Univariate comparisons between long and short half-life cohorts were conducted for all variables of interest. Patients had different follow-up times, so outcomes were reported per person-year (PY). To account foroverdispersion in the data, we used a negative binomial distribution for the crude rates of hospitalization or composite hospitalization/ED events when comparing outcomes.

To control for baseline differences and adjust for real-time adherence to therapy, we conducted a partial likelihood Cox proportional hazards model with therapy gap as a time-dependent variable (updated daily). In a sensitivity analysis, we replaced gap length with another time-dependent adherence measure, medication possession ratio over the previous 90 days (MPR-90), updated daily.

We calculated the number of patients who would need to be treated with long half-life medications instead of short half-life medications for 6 months, 1 year, and 2 years to prevent one additional event. At each time point (t), the number needed to treat (NNT) was determined using the survival probability of the short half-life cohort ($S_s(t)$) and the adjusted hazard ratio (h; long half-life vs. short half-life) with the following equation: $NNT = 1/\{[S_s(t)]^h - S_s(t)\}$.[7]

All data transformations and statistical analyses were performed using SAS© version 9.2 (SAS Institute, Cary, North Carolina).

Results

The long-half life and short half life groups had 1,479 and 837 individuals, respectively, and the groups had similar ages and Medicaid coverage types at baseline. Reflecting the Medicaid population, about 90% of both groups were blind/disabled. The long half-life group was 51.3% female, vs. 60.2% of the short half-life group. The long half-life group was 51.5% white, vs. 59.9% of the short half-life group (p<.001 for both comparisons). Year of index date also differed between groups, with 37.1% of long and 26.6% of short half-life medications prescribed in 2004 (p<.001). (Table 2)

Table 2. Patient Demographics, Benefit Type, and Index Year

Variable	Long Half-Life n = 1,479 (63.9%)	Short Half-Life n = 837 (36.1%)	All N = 2,316 (100.0%)	*P* Value
Age, in years; mean (SD)	40.5 (12.6)	40.6 (11.9)	40.5 (12.4)	0.82
		No. (%)		
Female	758 (51.3)	504 (60.2)	1,262 (54.5)	<.001
Race				<.001
White	762 (51.5)	501 (59.9)	1,263 (54.5)	
Black	584 (39.5)	272 (32.5)	856 (37.0)	
Other	133 (9.0)	64 (7.6)	197 (8.5)	
Medicaid coverage type				0.70
Capitated	453 (30.6)	250 (29.9)	703 (30.4)	
Fee-for-service	1,026 (69.4)	587 (70.1)	1,613 (69.6)	
Blind/disabled	1,345 (90.9)	748 (89.4)	2,093 (90.4)	0.22
With mental health/substance abuse coverage	1,453 (98.2)	828 (98.9)	2,281 (98.5)	0.20
Year of index date				<.001
2004	548 (37.1)	223 (26.6)	771 (33.3)	
2005	520 (35.2)	373 (44.6)	893 (38.6)	
2006	386 (26.1)	235 (28.1)	621 (26.8)	
2007	25 (1.7)	6 (0.7)	31 (1.3)	

A significantly lower unadjusted rate of hospitalization/ED visits for mental disorders was evident for long (0.74/patient-year) versus short (1.06/ patient-year) half-life antipsychotics (*P* <.001).

The unadjusted rate of hospitalization alone was also significantly lower for long (0.38/patient-year) versus short (0.52/patient-year) half-life antipsychotics (*P* =.005). (Table 3)

Table 3. Follow-up Years and Unadjusted Outcome Measures, Stratified by Cohort

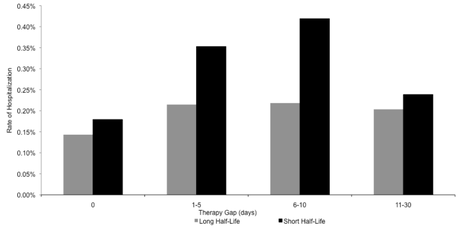
		Long Half-Life N = 1,479	Short Half-Life N = 837	All N = 2,316	*P* Value
Follow-up years	Mean	0.65	0.62	0.64	
	Total	959.9	518.8	1,478.7	
Hospitalization/ED visit for mental disorder(s)	No. of events	523	362	885	
	Events/PY[a]	0.74	1.06	0.85	<.001
Hospitalization/ED visit for schizophrenia	No. of events	386	237	623	
	Events/PY[a]	0.49	0.59	0.52	0.08
Hospitalization for mental disorder(s)	No. of events	318	214	532	
	Events/PY[a]	0.38	0.52	0.43	0.005
Hospitalization for schizophrenia	No. of events	261	160	421	
	Events/PY[a]	0.31	0.36	0.32	0.38

[a] Observation period was censored once the first event occurred.

As compared with short half-life antipsychotic drugs, the adjusted hazard ratio associated with long half-life medications was 0.80 (95% CI: 0.67-0.96) for psychiatric hospitalization and 0.77 (95% CI:0.67-0.88) for combined hospitalization/ED visits. Hospitalization/ED visits for schizophrenia were lower in the long half-life group, but the difference was not statistically significant. Across different gaps in therapy, hospitalization rates for mental disorders were higher in the short-acting group compared with the long-acting group. (Figure 1)

In a sensitivity analysis we replaced gap length with MPR in the model, and the results were similar. To test whether the group results were disproportionately impacted by individual drugs, we compared unadjusted outcomes across individual drugs. For the primary outcome of hospitalization or ED visit for mental disorders, the range of rates within the groups was narrow, with the rate for the long half-life group ranging from 0.74 to 0.76/ PY and for the short half-life group from 1.05 to 1.08/PY.

Figure 1. Rate of Hospitalization for Mental Disorders by Days of Therapy Gap



Treating 11 patients for 1 year with long, rather than short, half-life medications would avoid 1 hospitalization or ED visit for mental disorders (Table 4).

Table 4. Number Needed to Treat with Long Half-Life Medications to Prevent One Additional Event

Event	Length of treatment[a]	NNT Therapy Gap[b]
Hospitalization/ED for mental disorder(s)	6 months	12
	1 year	11
	2 years	10
Hospitalization/ED visit for schizophrenia	6 months	24
	1 year	19
	2 years	17
Hospitalization for mental disorder(s)	6 months	21
	1 year	16
	2 years	14
Hospitalization for schizophrenia	6 months	38
	1 year	27
	2 years	23

[a] Time from index date.
[b] Using adjusted hazard ratio from model with days of therapy gap as a measure of adherence.

Limitations

Medical and pharmacy claims are generated for administrative and reimbursement rather than clinical or research purposes

As with other claims datasets, information on healthcare encounters, prescription drug utilization, and diagnoses in Medicaid files are subject to coding errors and omissions

Use and adherence is not necessarily implied by receipt of services and filling of prescriptions

This study was conducted within the Medicaid setting and may not be generalizable to other settings

Conclusion

Following inpatient admission for schizophrenia, adherence with antipsychotic treatment is an important determinant of health service use in general and hospitalization in particular.

For a given level of medication adherence, schizophrenia patients taking atypical antipsychotics with longer half-lives were less likely to suffer the primary outcome of hospitalization/ED visit for mental disorders than patients taking atypical antipsychotics with shorter half-lives.

These findings support the hypothesis that atypical antipsychotics with longer half-lives are more "forgiving" of imperfect adherence than those with shorter half-lives.

Based on this study, it appears that outcomes may be improved in patients with schizophrenia who are treated with atypical antipsychotics, not just by increasing adherence, as has previously been shown, but also by choosing medications whose effect is less likely to be attenuated by imperfect adherence.

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