

# Hospitalization and Emergency Department Visits Among Patients Treated with Atypical Antipsychotics: Evidence from a Commercially Insured Population

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**KEY WORDS:** hospitalizations, emergency department, atypical antipsychotics

## ABSTRACT

**BACKGROUND:** The purpose of this study was to compare differences in hospitalization and emergency department (ED) use associated with the use of three popularly prescribed atypical antipsychotics: olanzapine (Zyprexa; Eli Lilly and Company, Indianapolis, IN); quetiapine (Seroquel; AstraZeneca, London, England); and risperidone (Risperdal; Janssen, L.P., Titusville, NJ).

**METHODS:** A retrospective analysis examined patients who had been diagnosed with a mental illness and initiated treatment with olanzapine (n=8,730), quetiapine (n=5,709), or risperidone (n=9,339) between July 1, 1998 and July 2, 2002, and had continuous insurance coverage from 6 months prior through 6 months post medication initiation. For each of the medications, differences in the mean number of hospitalizations

between the 6 month prior to initiation of medication to the 6 months post initiation were examined using paired *t*-tests, while differences in the rates of hospitalization and ED visits were examined using McNemer's tests. Differences among patients who initiated therapy with olanzapine, quetiapine, or risperidone were examined using analysis of covariance (ANCOVA), controlling for age, gender, region, and type of mental illness diagnosis. Results were also examined for subgroups of patients who were diagnosed with bipolar disorder or schizophrenia.

**RESULTS:** Patients who initiated treatment with olanzapine or risperidone had significantly higher rates of hospitalization (2.47% higher,  $P<0.0001$  for olanzapine; 1.71% higher,  $P<0.0001$  for risperidone) and ED visit rates (3.87% higher,  $P<0.0001$  for olanzapine; 4.69% higher,  $P<0.0001$  for risperidone) in the 6 months after initiation of medication than in the 6 months before. In addition, the mean number of hospitalizations was significantly higher for patients who

initiated therapy on olanzapine or risperidone (0.13 higher,  $P < 0.0001$  for olanzapine; 0.12 higher,  $P < 0.0001$  for risperidone) in the 6 months after initiation of therapy than during the 6 months before. In contrast, patients who initiated therapy with quetiapine had a significantly lower difference in the rates of hospitalization (4.62% lower,  $P < 0.0001$ ) and ED visits (2.98% lower,  $P < 0.0001$ ) and a significantly lower mean number of hospitalizations (0.08 lower,  $P < 0.0001$ ) during the 6 months after beginning quetiapine than during the 6 months pre-initiation.

**CONCLUSION:** Unlike olanzapine or risperidone, quetiapine may be associated with lower rates of hospitalizations and ED visits as well as a reduction in the mean number of hospitalizations after medication initiation.

## INTRODUCTION

The development of the class of medications known as atypical antipsychotics represented a significant change in the treatment of mental illness. While not without their side effects,<sup>1,3</sup> the atypicals, compared to conventional antipsychotics, have been associated with a lower incidence of extrapyramidal side effects,<sup>4,5</sup> and tardive dyskinesia,<sup>6,7</sup> as well as improved efficacy.<sup>8-10</sup> Such advantages associated with atypicals have resulted in an increase in treatment adherence<sup>11</sup> and improvements in quality of life.<sup>10-13</sup>

Originally approved by the Food and Drug Administration (FDA) for the treatment of schizophrenia, most of the atypical medications have also received approval by the FDA for the treatment of bipolar mania. While the atypicals have been found to have advantages over the older, conventional antipsychotics and are being generally used for multiple indications, it is important to note that there may be important differences among the atypical antipsychotics.

For example, research has suggested that patients treated with olanzapine (Zyprexa; Eli Lilly and Company, Indianapolis, IN) or clozapine (Clozaril; Novartis, New York, NY) may be at higher risk for the development of weight gain and/or diabetes<sup>2,3</sup> than other atypical antipsychotic users, while ziprasidone (Geodon; Pfizer, New York, NY) is the only atypical antipsychotic that has been found to be associated with QT interval prolongation.<sup>14,15</sup>

In addition to differences in side effect profiles, there may also be differences in efficacy. Clinical trial comparisons between olanzapine and risperidone (Risperdal; Janssen, L.P, Titusville, NJ) have found that treatment with olanzapine may be more effective at maintaining control over negative symptoms<sup>16</sup> and may result in significantly larger improvements in quality of life,<sup>17</sup> while treatment with risperidone may result in greater reductions in the severity of positive and affective symptoms.<sup>18</sup> In addition, clinical trials that have compared quetiapine (Seroquel; AstraZeneca, London, England) and risperidone have generally found greater improvements in depression scores, as well as a more favorable extrapyramidal symptoms (EPS) profile<sup>19,20</sup> associated with the use of quetiapine.

The purpose of this study was to compare in a naturalistic environment the differences in outcomes associated with the use of the three most popularly prescribed medications in this class: olanzapine, quetiapine, and risperidone. A retrospective claims database was used to examine the differential impact of a specific atypical antipsychotic initiation on hospitalization and emergency department (ED) use, two outcomes that have been shown to be key indicators of relapse and high costs among patients with mental illness.

## METHODS

The MedStat MarketScan Commercial

Claims and Encounters (CCE) database (Thomson MedStat; Ann Arbor, MI) provided the data for these analyses. The CCE database includes private sector health data from approximately 100 payers and contains data on clinical utilization, expenditures, and enrollment across inpatient, outpatient, prescription drug, and carve-out services. The CCE database links paid claims and encounter data to detailed patient information across sites and types of providers over time.

Given this database, patients were considered eligible for inclusion if they initiated therapy with either olanzapine, quetiapine, or risperidone between July 1, 1998 and July 2, 2002 (with the first such date identified as the index date) and had continuous insurance coverage, including outpatient prescription drug coverage from 6 months before (pre-period) to 6 months after (post-period) the index date. Of the 23,778 patients who met the above criteria, 8,730 had received olanzapine, 5,709 had received quetiapine, and 9,339 had received risperidone. In addition to examining all patients who initiated therapy with olanzapine, quetiapine, or risperidone, the analyses also focused on subgroups of patients who had been diagnosed with bipolar disorder or schizophrenia.

Differences in patient characteristics for individuals who initiated therapy on olanzapine, quetiapine, or risperidone were compared using *t*-tests for continuous variables and chi-square statistics for categorical variables. For each therapy group, differences in rates of hospitalization and ED visits between the pre-period and the post-period were examined using McNemer's tests, while differences in the mean number of hospitalizations were examined using paired-difference *t*-tests.<sup>21</sup> Differences in hospitalization and ED visit rates and the mean number of hospitalization between the pre-period and post-period

were also compared for individuals who initiated therapy on olanzapine, quetiapine, or risperidone. These studies used analysis of covariance (ANCOVA), controlling for the patient's age, gender, region of residence (northeast, north central, or west), and mental illness diagnosis (bipolar disorder, schizophrenia, dementia, or depression). A similar methodology was employed when examining the subgroups of patients diagnosed with bipolar disorder or schizophrenia, although these analyses did not control for mental illness diagnosis when comparing outcomes across types of medication.

All analyses were conducted using SAS Version 8.1.<sup>22</sup> Findings of a *P*-value  $\leq 0.05$  were considered to indicate statistically significant differences between the groups.

## RESULTS

### Comparison of Patient Characteristics across Cohorts

Table 1 presents the descriptive characteristics of all patients included in the analyses, categorized by the type of atypical antipsychotic used for treatment. The results indicate significant differences among the olanzapine, quetiapine, and risperidone cohorts with regards to both age and gender. Specifically, individuals who initiated therapy with risperidone were found to be significantly younger and more likely to be male than individuals who initiated on olanzapine or quetiapine. In contrast, patients who initiated therapy with olanzapine were significantly older than individuals who initiated on quetiapine or risperidone while patients who initiated on quetiapine were more likely to be female. Moreover, the results indicate differences in geographic location between the three cohorts.

Table 1 also illustrates significant differences among the cohorts with regard to diagnoses. For example,

**Table 1.** Patient Demographics by Medication

Variable	Olanzapine (N=8,730)	Quetiapine (N=5,709)	Risperidone (N=9,339)
Mean Age	40.37 <sup>†</sup>	39.61 <sup>†‡</sup>	37.39 <sup>‡</sup>
Gender (%)			
Female	58.47 <sup>†</sup>	61.44 <sup>†‡</sup>	54.98 <sup>‡</sup>
Location (%)			
North East	24.93	25.61	25.55
North Central	26.15	26.32	26.31
South	42.70	42.11	42.19
West	6.11	5.80	5.78
Diagnosis (%)			
Schizophrenia	8.16	7.01 <sup>‡</sup>	7.74 <sup>‡</sup>
Bipolar	27.97 <sup>†</sup>	25.04 <sup>†</sup>	24.77 <sup>†</sup>
Dementia	1.51	1.17 <sup>‡</sup>	1.70 <sup>‡</sup>
Depression	46.59 <sup>†</sup>	44.42 <sup>†‡</sup>	46.09 <sup>‡</sup>
Mean dose	14.76	347.26	3.56

<sup>†</sup>Significant difference between olanzapine and risperidone cohort ( $P<0.05$ )  
<sup>†</sup>Significant difference between olanzapine and quetiapine cohort ( $P<0.05$ )  
<sup>‡</sup>Significant difference between quetiapine and risperidone cohort ( $P<0.05$ )

Differences in continuous variables were examined using *t*-tests, while differences in categorical variables were examined using chi-square tests.

patients who initiated therapy with olanzapine were more likely to have been diagnosed as bipolar compared to patients who initiated therapy on either risperidone or quetiapine. Patients who initiated therapy with quetiapine were significantly less likely to have been diagnosed as depressed compared to patients who initiated therapy with olanzapine or risperidone and were significantly less likely to have been diagnosed as schizophrenic than patients who initiated therapy with risperidone.

### **Changes in Outcomes Between the Pre-Period and Post-Period**

Table 2 presents the results from examining whether there is a significant change in hospitalization and ED visits rates and in the mean number of hospitalizations when comparing the 6

months prior to initiation of olanzapine, quetiapine, or risperidone to the 6 month post-period. The results indicate that, in all cases, changes in all outcomes are significantly different in the post-period compared to the pre-period. When examining all patients, results indicate that patients who initiated olanzapine or risperidone therapy experienced significantly higher rates of hospitalization (2.47%,  $P<0.0001$ ; 1.71%,  $P<0.0001$ , respectively) and ED visits (3.87%,  $P<0.0001$ ; 4.69%,  $P<0.0001$ , respectively) as well as increases in the mean number of hospitalizations (0.13,  $P<0.0001$ ; 0.12,  $P<0.0001$ , respectively) during the post-period compared to the pre-period, while individuals who initiated therapy with quetiapine showed significant reductions in these measures of resource utilization (4.37% reduction in

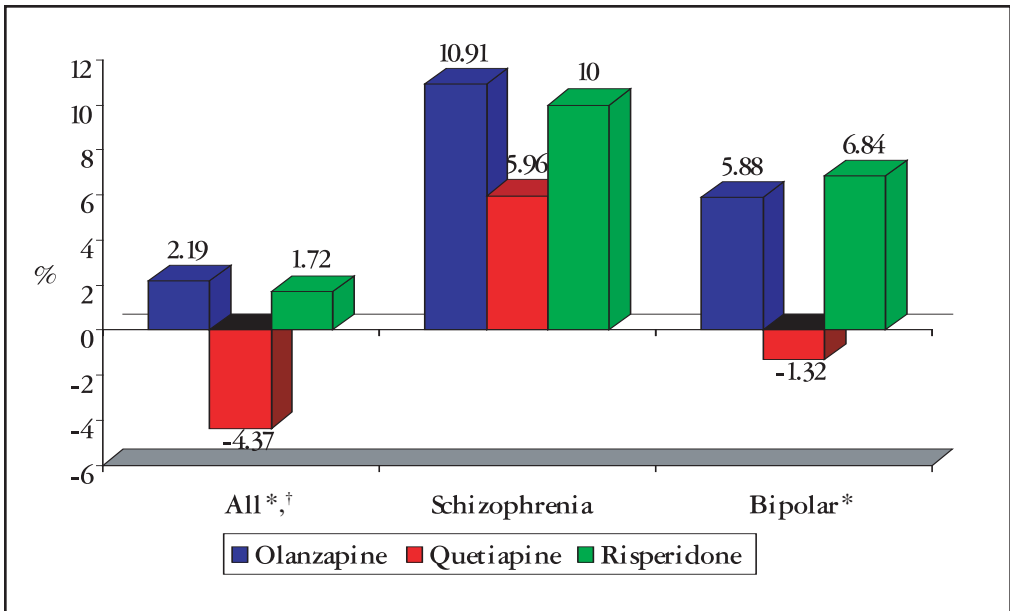
**Table 2.** Differences in Hospitalization and Emergency Department (ED) Visits Between Pre- and Post-Periods

Variable	All Individuals					
	Olanzapine (n=8,730)		Quetiapine (n=5,709)		Risperidone (n=9,339)	
	Estimate	P-value	Estimate	P-value	Estimate	P-value
Difference in % hospitalized	2.47	<0.0001	-4.62	<0.0001	1.71	<0.0001
Difference in % visited ED	3.87	<0.0001	-2.98	<0.0001	4.69	<0.0001
Difference in number of hospitalizations	0.13	<0.0001	-0.08	<0.0001	0.12	<0.0001
Variable	Individuals Diagnosed with Schizophrenia					
	Olanzapine (n=712)		Quetiapine (n=403)		Risperidone (n=723)	
	Estimate	P-value	Estimate	P-value	Estimate	P-value
Difference in % hospitalized	11.09	<0.0001	4.96	0.0241	10.37	<0.0001
Difference in % visited ER	5.20	0.0030	-0.75	0.9022	5.81	0.0014
Difference in # hospitalizations	0.46	<0.0001	0.11	0.0421	0.55	<0.0001
Variable	Individuals Diagnosed with Bipolar Disorder					
	Olanzapine (n=2,442)		Quetiapine (n=1,436)		Risperidone (n=2,313)	
	Estimate	P-value	Estimate	P-value	Estimate	P-value
Difference in % hospitalized	6.15	<0.0001	-2.38	0.3385	7.22	<0.0001
Difference in % visited ED	5.41	<0.0001	-2.73	0.0364	5.58	<0.0001
Difference in number of hospitalizations	0.29	<0.0001	-0.02	0.5398	0.37	<0.0001
Paired-difference <i>t</i> -tests were used to examine whether the difference in hospitalizations between the pre-period and post-period was statistically significant.						
McNemer's tests were used to examine whether the difference in rates of hospitalization or ED visits between the pre-period and post-period was statistically significant.						

hospitalization rates,  $P < 0.0001$ ; 2.98% reduction in ED visit rates,  $P < 0.0001$ ; 0.08 fewer hospitalization,  $P < 0.0001$ ).

These findings generally held true when examining the subgroup of patients diagnosed with bipolar disorder or schizophrenia. However, patients treated with quetiapine and diagnosed

as schizophrenic had a significantly higher probability of hospitalization (4.96%,  $P = 0.0241$ ) and significantly more hospitalizations (0.11,  $P = 0.0421$ ) in the post-period compared to the pre-period. In addition, patients who initiated treatment with quetiapine and were diag-



**Figure 1.** Percentage of patients hospitalized

\*Significant differences between olanzapine and quetiapine cohort ( $P \leq 0.05$ )

†Significant differences between risperidone and quetiapine cohort ( $P \leq 0.05$ )

Analysis of covariance (ANCOVAs) controlling for age, gender, region and mental illness diagnosis

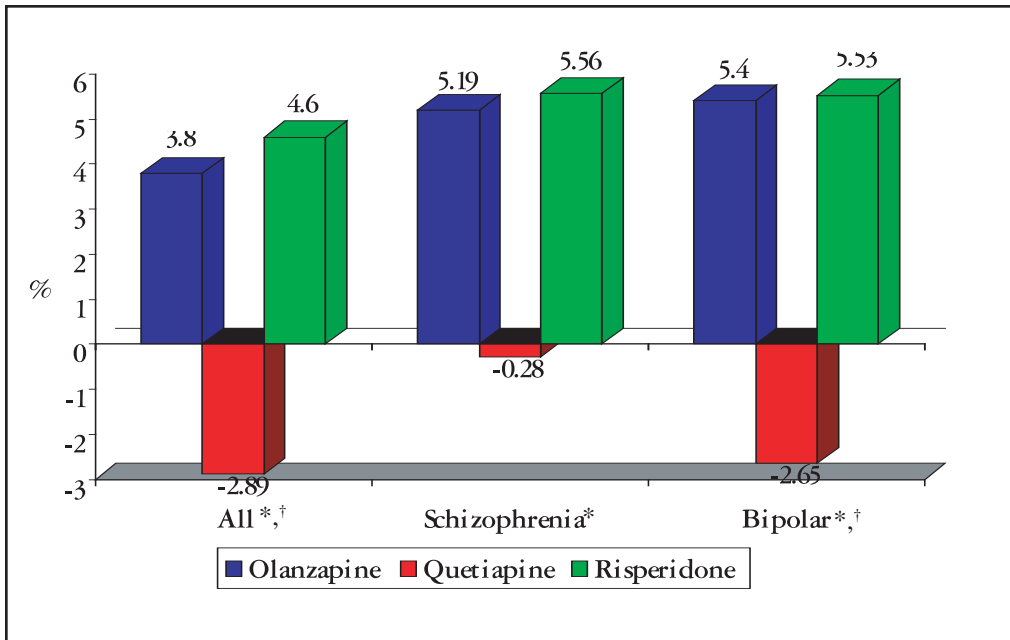
nosed with schizophrenia had no significant difference in ED visit rates (-0.75%,  $P=0.9022$ ), while patients diagnosed with bipolar disorder who initiated treatment with quetiapine had no significant difference in the number of hospitalizations (-0.02,  $P=0.5398$ ) when comparing the 6 months before initiation to the 6 months after.

### Comparing Outcomes Across Cohorts

ANCOVAs which control for age, gender, region, and mental illness diagnoses were used to examine differences in hospitalization rates (Figure 1) and ED visits (Figure 2) as well as differences in the mean number of hospitalizations (Figure 3) from the post-period to the pre-period among individuals who were treated with olanzapine, quetiapine, or risperidone. When examining all patients, changes in the rates of hospitalizations and ED visits as well as in the mean number of hospitalizations were significantly lower in the quetiapine

cohort compared to either the olanzapine or risperidone cohort. For example, as Figure 1 illustrates, patients treated with quetiapine had a 4.37% reduction in the rate of hospitalization when comparing the 6 months before initiation to the 6 months after, while patients initiated with olanzapine or risperidone had significant increases in hospitalization rates (2.19% and 1.72%, respectively).

The figures also show how changes in hospitalizations and ED use from the 6 months prior to the 6 months post initiation on medication differs for patients who have been diagnosed with either schizophrenia or bipolar disorder. The results for patients diagnosed with bipolar disorder are similar to the findings for all patients. Namely, compared to patients who initiated therapy with either olanzapine or risperidone, patients who initiated therapy with quetiapine had significantly less hospitalizations and ED visits as well as a



**Figure 2.** Percentage of patients who visited emergency departments

<sup>\*</sup>Significant differences between olanzapine and quetiapine cohort ( $P \leq 0.05$ )

<sup>†</sup>Significant differences between risperidone and quetiapine cohort ( $P \leq 0.05$ )

ANCOVAs controlling for age, gender, region and mental illness diagnosis

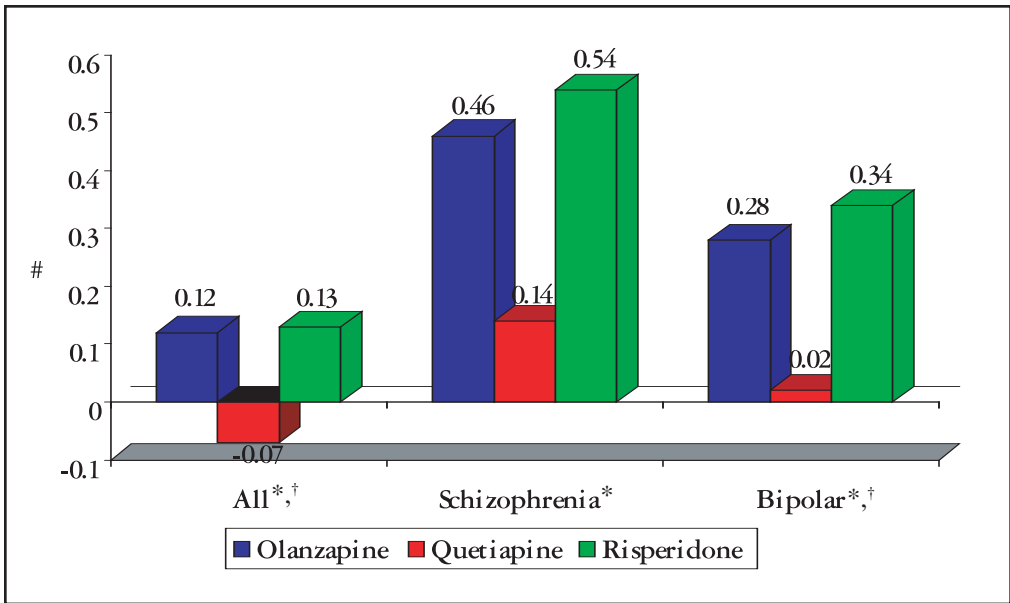
significantly lower mean number of hospitalizations. Among patients diagnosed with schizophrenia, patients who initiated therapy with quetiapine had a significantly lower change in the mean number of hospitalizations compared to individuals who initiated therapy with olanzapine or risperidone and a significantly lower change in the rate of ED visits compared to patients who initiated therapy with olanzapine. In all cases, there was no statistical difference in outcomes when comparing patients treated with olanzapine to those treated with risperidone.

## DISCUSSION

Results from this retrospective database analysis indicate that there are differences in hospitalization and ED use when comparing patients pre- and post-initiation on atypical antipsychotics. Specifically, patients who initiated queti-

apine therapy experienced significant reductions in hospitalization and ED use, while patients who initiated olanzapine or risperidone therapy experienced significant increases in the utilization of same resources. When comparing patient outcomes between the pre- and post-periods based upon their medication prescribed, there were generally no differences between the olanzapine and risperidone cohorts, while the quetiapine cohort had significantly lower risk of hospitalization or an ED visit, as well as a significantly lower mean number of hospitalizations compared to the olanzapine or risperidone cohorts. These results were similar for patients who initiated therapy with one of the atypical antipsychotics and were diagnosed with schizophrenia or bipolar disorder.

Prior research has demonstrated that proxies of relapse, such as hospital readmission, do not differ considerably



**Figure 3.** Number of hospitalizations

\*Significant differences between olanzapine and quetiapine cohort ( $P \leq 0.05$ )

†Significant differences between risperidone and quetiapine cohort ( $P \leq 0.05$ )

ANCOVAs controlling for age, gender, region and mental illness diagnosis

from results measured by clinical instruments, such as the Positive and Negative Syndrome Scale (PANSS).<sup>23</sup> Given this finding, it is not surprising that researcher have used hospitalization to examine patient relapse and drug efficacy.<sup>24-26</sup> In addition, hospitalization has been shown to be a significant component of the direct medical costs associated with the treatment of schizophrenia,<sup>27,28</sup> bipolar disorder,<sup>29</sup> and dementia.<sup>30</sup> Research has also shown that use of the ED is a particular problem among patients with a diagnosis of mental illness being found to be a risk factor for repeat visits to the ED.<sup>31</sup> As such, therapies that can reduce patient use of the hospital and emergency departments may not only lead to improved patient outcomes, but also may have significant cost implications.

The finding of significant reductions in hospitalizations and ED visits associated with the use of quetiapine is largely

consistent with clinical trial evidence that has examined the safety and efficacy of quetiapine. For example, prior research has shown that quetiapine is associated with improved positive, negative, and depressive symptoms, as well as reduced agitation, aggression, and hostility.<sup>32</sup> In addition, research has also demonstrated an association between the use of quetiapine and reductions in hospitalization.<sup>33</sup> In our research, there was a 4.37% reduction in the number of patients who were hospitalized in the 6 months after initiating quetiapine therapy relative to the 6 months before. In contrast, patients who initiated therapy on olanzapine or risperidone were found to have significantly more hospitalizations and ED visits when comparing the 6 months after initiation to the 6 months before. While this finding appears to be inconsistent with published research which has examined this issue,<sup>34-36</sup> the sample used in this study is more broad-



ly defined than prior research. However, the results reported are robust to an examination of just the subset of patients who are diagnosed with either schizophrenia or bipolar disorder.

Prior research that has directly compared the atypical medications has generally found mixed results. For example, comparisons of olanzapine and risperidone that are favorable to olanzapine have found lower costs associated with the use of olanzapine, with differences in costs being driven by hospitalizations<sup>37</sup> and significantly fewer hospitalizations associated with olanzapine.<sup>38</sup> In contrast, other research has found significantly shorter lengths of hospital stays when comparing patients who use risperidone to those who use olanzapine<sup>15,39,40</sup> or no difference in readmission risk or hospital length of stay between the two drugs.<sup>41-43</sup> The finding in our study of significant differences between patients treated with quetiapine compared to those treated with risperidone is largely consistent with findings from the QUEST study, which also focused on patients with a broad range of psychotic symptoms.<sup>20</sup> Specifically, the QUEST study found that quetiapine was similar to risperidone for the treatment of psychotic symptoms and overall tolerability, and that it was more effective for depressive symptoms and may have a more favorable EPS profile.<sup>20</sup> These relative advantages of quetiapine may result in significant differences in hospitalization and ED use.

Strengths of this study include a relatively recent time frame and incorporation of a wide range of patients who are actually treated with atypical antipsychotics. However, as with any research, it is important that the findings be interpreted in the context of the limitations of the study design. While the study benefits from a geographically diverse, relatively recent sample, this sample is most likely not generalizable to other popu-

lations. For example, this sample consists solely of patients who are privately insured. However, a large proportion of patients diagnosed with mental illness, particularly those who are diagnosed with schizophrenia, are insured via Medicaid instead of private insurance. In addition, the use of diagnostic codes to identify patients is not as rigorous as formal diagnostic assessments for identifying patients with mental illness, and the use of medical claims data does not allow for the analysis of more detailed instruments, such as patient assessments of quality of life, physical functioning, or levels of disability. Finally, it is important to note that the analysis focused exclusively on hospitalizations and emergency department use as indicators of resource use and patient relapse, and hence did not include other issues, such as direct medical costs or caregiver burden.

## CONCLUSION

In summary, this paper presents the results of a retrospective, naturalistic study that examines hospitalizations and ED visits pre- and post-initiation on olanzapine, quetiapine, and risperidone. After controlling for demographic characteristics and mental illness diagnoses, results indicate that there are significant differences among the atypicals with regard to their impact on hospitalization and ED visits. Specifically, patients who were initiated on quetiapine therapy experienced significantly fewer hospitalizations and ED visits, as well as a significantly lower mean number of hospitalizations. In contrast, patients who began olanzapine or risperidone therapy had significantly higher rates of hospitalization or ED visits and a significantly higher mean number of hospitalizations in the 6 months after beginning therapy than during the 6 months before. Given the large costs associated with hospitalizations and ED use, as well as the evidence suggesting that the use

of such services may indicate a patient relapse, these findings have important implications for the successful treatment of patients diagnosed with mental illness. Further studies are warranted to examine the robustness of these results.

## ACKNOWLEDGEMENTS

The authors would like to acknowledge the assistance of Patricia Platt in the technical editing of this manuscript. Funding for her work was provided by HealthMetrics Outcomes Research, LLC.

## DISCLOSURE STATEMENT

Funding for this study was provided by AstraZeneca.

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