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All-cause hospitalization and associated costs in patients with schizophrenia or bipolar disorder initiating long-acting injectable antipsychotics

Tingjian Yan, Mallik Greene, Eunice Chang, Ann Hartry, Maëlys Touyac and Michael S. Broder

ABSTRACT

Objective: To compare all-cause hospitalization and associated costs among patients with schizophrenia or bipolar disorder (BD) treated with long-acting injectable antipsychotics (LAIs).

Methods: The Truven MarketScan Medicaid claims database was used to identify patients with schizophrenia; MarketScan Medicaid and commercial claims databases were used to identify BD. Adult patients with ≥1 LAI claim from January 1, 2013–June 30, 2014 (ID period) were identified. The first day of LAI initiation was the index date; patients were followed for ≥1 year. Logistic and general linear regression models were used to estimate the risk of hospitalization and associated costs.

Results: Adjusted analyses showed that, in the schizophrenia cohort, risks of hospitalization were statistically significantly higher in the haloperidol [OR (95% CI) = 1.51 (1.03–2.16); HR (95% CI) = 1.35 (1.05–1.73)] and risperidone [OR (95% CI) = 1.58 (1.07–2.33); HR (95% CI) = 1.33 (1.01–1.74)] cohorts than in the aripiprazole once monthly extended release (AOM 400) cohort. Similarly, in patients with BD, risks of hospitalization were significantly higher in haloperidol [OR (95% CI) = 1.49 (1.01–2.19); HR (95% CI) = 1.33 (1.03–1.73)] and risperidone [OR (95% CI) = 1.78 (1.19–2.66); HR (95% CI) = 1.33 (1.01–1.75)] than in AOM 400. No statistically significant differences in hospitalization costs were observed in either disease group.

Conclusions: Although the study results may be subject to confounding variables that are not contained in claims databases, such as disease severity, it appears that AOM400 may be more effective than haloperidol and risperidone LAIs among patients with schizophrenia or BD.

Introduction

Schizophrenia and bipolar disorder (BD) are serious and chronic mental disorders, affecting 1.1% and 2.6% of the US adult population, respectively. They can have a devastating impact on patients, in terms of personal suffering and reduced quality-of-life, and on society, in terms of substantial economic burden on the US healthcare system. The estimated annual direct and indirect healthcare costs for treating schizophrenia were over $155 billion in 2013. Persons with BD incurred $200 billion in combined direct and indirect healthcare cost in 2015.

Hospitalization, a useful proxy for relapse, is one of the major drivers of healthcare costs, contributing up to two-thirds of the total direct costs of treating patients with schizophrenia and over a quarter of the total direct costs of treating patients with BD. In addition, relapses can have devastating repercussions, including reduced quality-of-life and increased caregiver burden, and worse disease prognosis. Preventing hospitalization is critical in the successful management of schizophrenia and BD.

Antipsychotics are the cornerstone of pharmacological treatment of schizophrenia. Compared with oral formulations, long-acting injectable antipsychotics (LAIs) offer several advantages, such as no need for daily administration, reliable monitoring of treatment adherence, and an increased opportunity for the treatment team to intervene appropriately if a patient misses a dose. Six LAIs, with different formulations, are currently available and approved by the US Food and Drug Administration (FDA) for the treatment of schizophrenia. These include aripiprazole once monthly extended release (AOM 400), aripiprazole lauroxil (aripiprazole lauroxil-LAI), fluphenazine decanoate (fluphenazine-LAI), haloperidol decanoate (haloperidol-LAI), olanzapine pamoate (olanzapine-LAI), paliperidone palmitate, 4-week (paliperidone-LAI), paliperidone palmitate, 12-week (paliperidone 12-week-LAI), and risperidone microspheres (risperidone-LAI). Administration schedules range from biweekly to every 3 months. Antipsychotics, as monotherapy or as adjunctive therapy to mood stabilizers, have also been increasingly used to treat BD. AOM 400 and risperidone-LAI are the only two approved LAIs for the maintenance-treatment of bipolar I disorder in the US, with AOM 400 recently approved in July 2017 for the maintenance treatment of BD type 1. Previous studies have shown that patients with BD have used AOM 400 and other LAIs off-label.
Current guidelines recommend that clinicians should consider LAIs in patients who are inadequately adherent to antipsychotics. The literature on the clinical effectiveness and economic impact of selecting one LAI vs another in reducing hospitalization and associated costs is limited. Prior studies have not included all recently approved LAIs, such as AOM 400. The aim of the current study was to evaluate all-cause inpatient healthcare utilization and associated costs for two separate populations—patients with schizophrenia and patients with BD—who were treated with different LAIs.

Methods

Data source and study design

To identify patients with schizophrenia, administrative claims data from the Truven Health Analytics MarketScan Medicaid claims database were used. This database includes demographic and clinical information, inpatient and outpatient utilization data and outpatient prescription data for 40 million Medicaid enrollees from multiple geographically dispersed states. Most patients with schizophrenia are insured through the Medicaid and Medicare programs and patients that are not may differ systematically (e.g. be less severely ill); thus, commercially insured patients with schizophrenia were not included in this analysis. To ensure complete medication claims histories, patients with Medicare dual-eligibility and those without mental health coverage were excluded.

To identify patients with BD, claims data from both Truven Medicaid and commercial databases were analyzed. The MarketScan commercial database includes medical and pharmacy claims for nearly 62.9 million individuals and their dependents who are covered through employer-sponsored private health insurance plans.

The data used for the two analyses were from January 1, 2012 through June 30, 2015. All data were compliant with the Health Insurance Portability and Accountability Act (HIPAA) of 1996. Institutional review board approval was not required.

Sample selection

Among patients with at least one inpatient claim or two outpatient claims for schizophrenia (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM]: 295.xx) at any time during the entire study period, six mutually exclusive LAI cohorts were identified. The cohorts comprised patients with schizophrenia and who started one of the following available LAIs during the identification (ID) period (January 1, 2013 to June 30, 2014): AOM 400, fluphenazine-LAI, haloperidol-LAI, risperidone-LAI, olanzapine-LAI, and paliperidone-LAI. Two currently marketed LAIs (aripiprazole lauroxil-LAI and paliperidone 12-week-LAI) were approved after the study end date and were not included. The index date was defined as the earliest occurrence (the first date) of a claim for one of the LAI therapies of interest during the ID period. The LAI observed on the index date was defined as the index therapy. Patients were excluded if they had claims for non-index LAI therapies in the 1-year prior to index (baseline period), or if they lacked continuous enrollment for 12-months pre- and 12-months post-index. Patients were followed for at least 1 year until the end of enrollment or study end, whichever occurred first. The first diagnosis of schizophrenia was required to be before the index date.

Analogous patient selection and cohort identification criteria were applied to identify the group of patients with BD (ICD-9-CM: 296.0x, 296.1x, 296.4x, 296.6x, 296.7x, 296.8x) who initiated LAIs.

Outcome measures

The outcome measures included in the study were all-cause hospitalization and associated costs, as well as risk of and time to first all-cause hospitalization. Hospitalization rates and associated costs were reported during the 1-year post-index period. The long-term risk of all-cause hospitalization during the entire follow-up period (≥365 days) was also reported. Outcomes were reported separately for schizophrenia and BD groups.

Statistical analysis

Descriptive analyses were performed to assess differences among the selected LAI cohorts across baseline covariates. Specifically, chi-square tests were used for categorical variables and two sample t-tests were used for continuous variables. Logistic regression and general linear regression models were conducted to estimate adjusted all-cause hospitalization rates and associated costs during the 1-year...
post-index period, controlling for baseline covariates, including age, gender, race (White vs non-White for the group of patients with schizophrenia), Charlson comorbidity index\textsuperscript{24,25}, number of chronic conditions\textsuperscript{26}, any baseline inpatient hospitalization or ED visits, depression, anxiety, BD (schizophrenia for the group of patients with BD), and any use baseline psychiatric or somatic medication use. A Cox regression model was conducted to estimate risks of all-cause inpatient hospitalization during the entire follow-up, adjusting for the baseline covariates mentioned above. All data transformations and statistical analyses were performed using SAS version 9.4.

Results

Sample description

Of the 79,826 patients with schizophrenia identified from the Truven Medicaid database, 2,861 initiated an LAI and met the study selection criteria. Due to the small sample size (n = 54), patients with olanzapine-LAI use were excluded. A total of 2,807 patients were, therefore, included in the schizophrenia analytic sample.

Of the 381,369 patients with BD identified from the Truven Commercial and Medicaid databases, 1,672 initiated an LAI and met the study selection criteria. Patients treated with fluphenazine-LAI (n = 97) and olanzapine-LAI (n = 35) were excluded due to the small sample sizes, leaving 1,540 patients in the BD analytic sample (Figure 1).

Baseline characteristics

Table 1 shows patient characteristics at baseline. Of the identified Medicaid patients with schizophrenia, 258 initiated AOM 400, 186 fluphenazine-LAI, 741 haloperidol-LAI, 1,235 paliperidone-LAI, and 387 risperidone-LAI. The mean age for the overall sample was 40 years, 43.2% of patients were female, 57.8% were African American, and the most common comorbidities were substance abuse (52.4%), depression (45.2%), and hypertension (42.8%).

Compared with other LAI users with schizophrenia, AOM 400 users were statistically younger, were more likely to be White, and had lower rates of hospitalization and ED use at baseline (p < 0.05 for all comparisons).

In the analytic sample for BD, 224 initiated AOM 400, 324 haloperidol-LAI, 741 paliperidone-LAI, and 251 risperidone-LAI. Compared with other LAI users with BD, AOM 400 users were statistically younger with a mean age of 34 years, and had lower rates of hospitalization and ED use at baseline (p < 0.05) (Table 1).

Risks of all-cause hospitalization

For the group of patients with schizophrenia, AOM 400 users had the lowest, unadjusted hospitalization rate (24.0%) during the 1-year post-index period, although there was no statistically significant difference in hospitalization rates across the LAI cohorts (p = 0.12). Further adjusting for differences in

\begin{table}
\centering
\begin{tabular}{|c|c|}
\hline
Base LAI Cohort & Hospitalization Rate \\
\hline
AOM 400 & 24.0% \\
Fluphenazine-LAI & 27.8% \\
Haloperidol-LAI & 30.0% \\
Paliperidone-LAI & 32.0% \\
Risperidone-LAI & 34.0% \\
\hline
\end{tabular}
\end{table}

...
Results for the group of patients with BD were similar. During the 1-year post-index and entire follow-up periods, compared with the AOM 400 cohort, the risks of having any inpatient hospitalization were significantly higher in the haloperidol-LAI (OR [95% CI] = 1.49 (1.01–2.19); HR [95% CI] = 1.33 (1.03–1.73)) and risperidone-LAI (HR [95% CI] = 1.33 (1.01–1.74)) cohorts (Table 2).

Results for the group of patients with BD were similar. During the 1-year post-index and entire follow-up periods, compared with the AOM 400 cohort, the risks of having any inpatient hospitalization were significantly higher in the haloperidol-LAI (OR [95% CI] = 1.49 (1.01–2.19); HR [95% CI] = 1.33 (1.03–1.73)) and risperidone-LAI (OR [95% CI] = 1.33 (1.01–1.75)) cohorts. Paliperidone-LAI users also had a higher risk of being hospitalized than AOM 400 users, but the differences were not statistically significant (p > 0.05).

All-cause hospitalization costs

Table 3 shows the unadjusted and adjusted hospitalization costs among hospitalized patients.

For hospitalized patients with schizophrenia (n = 854), the unadjusted mean hospitalization costs were numerically lower in AOM 400 users than in other LAI users during the 1-year post-index period. However, the differences were not statistically significant. Results from the general linear regression confirmed this finding. The adjusted mean all-cause hospitalization costs were lowest in the AOM 400 cohort ($25,697 (23,034–28,360)), followed by haloperidol-LAI ($31,584 (27,962–35,206)), paliperidone-LAI ($33,240 (28,621–37,861)), and fluphenazine-LAI ($37,338 (32,710–42,000)), although differences were not statistically significant.

For the group of patients with BD, the adjusted mean all-cause hospitalization costs among hospitalized patients (n = 597) were also lowest numerically in the AOM 400 cohort ($26,002 (29,231–32,771)), followed by haloperidol-LAI ($30,811 (27,244–34,378)), paliperidone-LAI ($30,833 (25,697–35,968)), risperidone-LAI ($31,584 (27,962–35,206)), and fluphenazine-LAI ($37,338 (32,710–42,000)), although differences were not statistically significant (p > 0.05) (Table 3).
Table 2. Unadjusted all-cause hospitalization rate and risksa of all-cause hospitalization.

<table>
<thead>
<tr>
<th>Schizophrenia</th>
<th>Unadjusted all-cause hospitalization rates in 1-year post-index period</th>
<th>Risk of all-cause hospitalization in 1-year post-index periodb</th>
<th>Risk of all-cause hospitalization in the entire follow-up periodc</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>p-value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>LAIs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AOM 400 (reference)</td>
<td>24.0%</td>
<td>0.117</td>
<td>–</td>
</tr>
<tr>
<td>Fluphenazine-LAI</td>
<td>31.2%</td>
<td>–</td>
<td>1.35 (0.85–2.13)</td>
</tr>
<tr>
<td>Haloperidol-LAI</td>
<td>30.6%</td>
<td>–</td>
<td>1.51 (1.05–2.16)</td>
</tr>
<tr>
<td>Paliperidone-LAI</td>
<td>29.7%</td>
<td>–</td>
<td>1.33 (0.94–1.87)</td>
</tr>
<tr>
<td>Risperidone-LAI</td>
<td>33.9%</td>
<td>–</td>
<td>1.58 (1.07–2.33)</td>
</tr>
<tr>
<td>Bipolar Disorder</td>
<td>n = 1,540</td>
<td>n = 1,540</td>
<td>n = 1,540</td>
</tr>
<tr>
<td>LAIs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AOM 400 (reference)</td>
<td>31.3%</td>
<td>&lt;0.001</td>
<td>–</td>
</tr>
<tr>
<td>Haloperidol-LAI</td>
<td>44.4%</td>
<td>–</td>
<td>1.49 (1.01–2.19)</td>
</tr>
<tr>
<td>Paliperidone-LAI</td>
<td>36.2%</td>
<td>–</td>
<td>1.11 (0.79–1.57)</td>
</tr>
<tr>
<td>Risperidone-LAI</td>
<td>45.8%</td>
<td>–</td>
<td>1.78 (1.19–2.66)</td>
</tr>
</tbody>
</table>

Abbreviations: OR, odds ratio; HR, hazards ratio; LAI, long-acting injectable.
aAdjusted for age group, gender, race (White vs non-White), Charlson comorbidity index, number of chronic conditions, any baseline inpatient hospitalization or ED visit, depression, anxiety, bipolar disorder/schizophrenia, any use baseline psychiatric medication use, and any baseline somatic medication use.
bLogistic regression model.
cCox regression model.

Table 3. Unadjusted and adjusted all-cause inpatient hospitalization costs among hospitalized patients during the 1-year post-index period.

<table>
<thead>
<tr>
<th>Schizophrenia</th>
<th>Unadjusted inpatient hospitalization costs among hospitalized patients, Mean (SD)</th>
<th>p-value</th>
<th>Adjusteda inpatient hospitalization costs among hospitalized patients, Mean/Rate (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AOM 400b (n = 62)</td>
<td>$23,893 (35,718)</td>
<td>0.609</td>
<td>$25,616 (13,099–38,133)</td>
<td>0.797</td>
</tr>
<tr>
<td>Fluphenazine-LAI (n = 58)</td>
<td>$38,639 (58,574)</td>
<td>0.551</td>
<td>$37,338 (24,418–50,259)</td>
<td>0.797</td>
</tr>
<tr>
<td>Haloperidol-LAI (n = 227)</td>
<td>$31,578 (38,052)</td>
<td>0.551</td>
<td>$30,811 (24,274–37,348)</td>
<td>0.797</td>
</tr>
<tr>
<td>Paliperidone-LAI (n = 367)</td>
<td>$30,456 (39,612)</td>
<td>0.551</td>
<td>$30,833 (23,697–35,968)</td>
<td>0.797</td>
</tr>
<tr>
<td>Risperidone-LAI (n = 131)</td>
<td>$31,607 (39,299)</td>
<td>0.551</td>
<td>$31,584 (22,986–40,183)</td>
<td>0.797</td>
</tr>
<tr>
<td>Bipolar Disorder</td>
<td>n = 597</td>
<td>n = 597</td>
<td>n = 597</td>
<td>n = 597</td>
</tr>
<tr>
<td>AOM 400b (n = 70)</td>
<td>$21,970 (33,768)</td>
<td>0.444</td>
<td>$26,002 (13,733–38,271)</td>
<td>0.675</td>
</tr>
<tr>
<td>Haloperidol-LAI (n = 144)</td>
<td>$32,062 (35,938)</td>
<td>0.444</td>
<td>$30,411 (21,978–38,845)</td>
<td>0.675</td>
</tr>
<tr>
<td>Paliperidone-LAI (n = 268)</td>
<td>$32,930 (66,188)</td>
<td>0.444</td>
<td>$33,240 (27,049–39,432)</td>
<td>0.675</td>
</tr>
<tr>
<td>Risperidone-LAI (n = 115)</td>
<td>$29,046 (38,687)</td>
<td>0.444</td>
<td>$27,937 (18,420–37,454)</td>
<td>0.675</td>
</tr>
</tbody>
</table>

Abbreviation: LAI, long-acting injectable.
aAdjusted for age group, gender, race (White vs non-White), Charlson comorbidity index, number of chronic conditions, any baseline inpatient hospitalization or ED visit, depression, anxiety, bipolar disorder/schizophrenia, any use baseline psychiatric medication use, and any baseline somatic medication use.
bReference.

discussion

Adapting for differences in baseline characteristics, compared with AOM 400 initiators, patients with schizophrenia initiating haloperidol-LAI and risperidone-LAI were 51% and 58% more likely to be hospitalized during the 1-year post-index period (p < 0.05), and 35% and 33% more likely to be hospitalized during the entire follow-up period (≥365 days) (p < 0.05). Compared with AOM 400, fluphenazine-LAI and paliperidone-LAI users had higher risks of hospitalization; however, differences were not statistically significant (p > 0.05). Among hospitalized patients, AOM 400 users had the numerically lowest hospitalization costs, although the differences were not statistically significant.

For the group of patients with BD, haloperidol-LAI and risperidone-LAI initiators were 49% and 78% more likely to be hospitalized during the 1-year post-index period (p < 0.05) and 33% and 33% more likely to be hospitalized during the entire follow-up period (≥365 days) (p < 0.05) than AOM 400 users. Paliperidone-LAI users had a higher risk of hospitalization than AOM 400 users; however, the difference was not statistically significant (p > 0.05). Hospitalized AOM 400 users had the lowest hospitalization costs, but the differences were not statistically significant. The positive findings in the AOM400 cohort relative to haloperidol-LAI and risperidone-LAI may be due to selection bias. As shown in the data, patients receiving LAI aripiprazole were significantly younger and less frequently utilized hospitalization or ED visit during the 1-year pre-index period. It is very likely that patients treated with AOM400 were less severe in psychopathology and functioning. We were unable to adjust these measures, due to lack of data in the claims database.

Hospitalization is a useful proxy for relapse when studying a naturalistic setting7. To reduce the risks of hospitalization or relapse, it is crucial to effectively address predisposing factors25. Partial adherence or non-adherence to antipsychotic medication increases the risk of relapse4. The majority of patients in this study used oral antipsychotics and were hospitalized or visited ED at baseline, suggesting that patients may have been poorly adherent to oral antipsychotics. A growing body of literature on the treatment of schizophrenia has shown that LAIs improve medication adherence, reduce...
inpatient hospitalization, and reduce costs compared with oral antipsychotics.28–30.

LAIIs are currently under-utilized31,32. The decision to initiate LAIs is influenced by attitudes of patients and clinicians.19,33. Patients may resist LAIs because of stigma, fear of injections, time constraints and costs34. Clinicians may be reluctant to prescribe LAIs due to their beliefs about side-effects, lack of evidence of superior efficacy and lack of practical knowledge about their use19. Optimal use of new formulation LAIs may require a substantial change in the general attitude towards LAIs as a treatment option19. In addition, given the general difficulties in the management of schizophrenia or BD and in identifying patients who are at-risk of relapse, no single treatment is currently effective for treating all patients. To take full advantage of current pharmacological therapies, multi-level approaches targeting more than one factor with more than one intervention are needed.

Based on our review of the literature, this is the first real-world study directly comparing the effectiveness of AOM 400 with other LAIs in preventing relapse. Previous studies directly comparing one LAI vs another focused on older LAIs, such as risperidone-LAI vs haloperidol-LAI15 or vs paliperidone-LAI6,37. A recent randomized clinical trial found that AOM 400 was superior to paliperidone-LAI in improving patients’ health-related quality-of-life and was associated with a favorable tolerability profile38. The impact of AOM 400 vs other LAIs on relapse and associated costs was not addressed in those studies.

This study had several limitations. First, schizophrenia and BD diagnoses were identified from health insurance claims, which are designed for reimbursement rather than research; misclassification, diagnostic uncertainty, or coding errors were possible. Nevertheless, health insurance claims data remain a valuable source of information as they contain a large sample of patients and include reliable measures of economic and utilization outcomes in a real-world setting. Second, lack of information on race in the MarketScan Commercial database used to identify patients with BD, further restricted us from including this potentially significant confounder in the multivariate analysis. Third, the goal of the study was to examine, on an intent to treat basis, outcomes associated with the initiation of various LAIs. Given this design, we did not adjust for dosing or tolerability of, or adherence to, the regimen initiated. We initiated this study to look broadly at two different indications and a wide variety of LAIs. The advantage of the current design is that it provides data on the question “what happens to patients initiated on different LAIs?”—rather than asking to what extent dosing, tolerability, or adherence impact treatment outcomes. Although these factors are related to outcomes, they may also be related to the treatment of interest. Additional research is needed to better understand the impact of these factors on outcome differences observed across the LAI agents. Fourth, due to the small sample size, some findings were not statistically significant. Future studies with larger sample sizes are warranted. Finally, results for the group of patients with schizophrenia are reflective of a multi-state Medicaid population, but may not be generalizable to non-Medicaid patient populations.

Conclusions

Although this was a retrospective study and cannot establish causality, it appears that AOM 400 may be more effective at reducing the risk of relapse for patients with schizophrenia or BD in a real-world setting as compared to haloperidol-LAI and risperidone-LAI. To take advantage of new therapeutic opportunities, clinicians treating patients with schizophrenia or BD may consider implementing programs that incorporate both pharmacological and non-pharmacological elements for better management of schizophrenia and BD.

Transparency

Declaration of funding

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Declaration of financial/other relationships

M. Greene is an employee of Otsuka Pharmaceutical Development and Commercialization Inc., Princeton, NJ. T. Yan, M.S. Broder, and E. Chang are employees of Partnership for Health Analytic Research, LLC, Beverly Hills, CA. A. Hartry and M. Touya are employees of Lundbeck, Deerfield, IL. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. Peer reviewers on this manuscript have received an honorarium from CMRO for their review work, but have no other relevant financial relationships to disclose.

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Previous presentations


References


