Antipsychotic adherence and emergency department utilization among patients with schizophrenia

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\textbf{ABSTRACT}

This retrospective cohort study evaluated the relationship between antipsychotic medication adherence and emergency department (ED) utilization for 7851 Medicaid patients with schizophrenia enrolled in Community Care of North Carolina (CCNC). Claims and pharmacy data from January to December 2015 were collected. Medication adherence was approximated using the medication possession ratio (MPR). Negative binomial regressions estimated the effect of antipsychotic adherence on rates of medical and psychiatric ED visits. The results demonstrated a statistically significant negative relationship between antipsychotic adherence and medical ED utilization. Non- and partially adherent patients (MPR < 0.80) had 1.61 times the rate of medical ED visits as fully adherent patients (MPR ≥ 0.80) (95% CI: 1.50–1.74, p-value < 0.001). The relationship between adherence and psychiatric utilization was small and not statistically significant. The most common diagnostic categories of ED visits were injuries and poisonings (16%), ill-defined symptoms (14%), and musculoskeletal conditions (12%). This study demonstrates a clear association between antipsychotic adherence and medical ED utilization, suggesting an important link between psychiatric management and medical utilization in patients with schizophrenia.

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1. Introduction

Patients with schizophrenia and other severe and persistent mental illnesses have high rates of costly acute care utilization (Billings and Mijanovich, 2007; Billings and Raven, 2013; Shim et al., 2014). Mental illness is among the most significant predictors of frequent emergency department (ED) use (Booth et al., 2011; Lin et al., 2015). However, patients with schizophrenia also have higher rates of ED and hospital utilization for non-psychiatric conditions than the general public (Jackson et al., 2015; Shim et al., 2014). These patients suffer from a disproportionate burden of undiagnosed and/or undertreated chronic illness, creating extremely complex health care needs (Hansen, 2012; Institute of Medicine (US) Committee on Crossing the Quality Chasm: Adaption to Mental Health and Addictive Disorders, 2006).

Adherence to an antipsychotic medication regimen is of particular concern for these patients, given that a large majority of experience gaps in medication use (Mojtahai et al., 2002). Non-adherent and partially adherent patients have predictably worse outcomes (Acosta et al., 2014; Weiden and Olsson, 1995). Multiple studies have shown that non-adherence is associated with higher rates of readmission, longer length of stay, and higher costs (Jiang and Ni, 2015; Offord et al., 2013; Weiden et al., 2004). The results are similar for psychiatric admissions and all-cause admissions. Less is known, however, about the relationship between non-adherence and the risk of visiting the emergency department for medical, non-psychiatric complaints. This link between poorly controlled mental illness and high acute-care medical utilization is becoming increasingly important for state Medicaid agencies as they seek to control costs through greater integration of care (Nardone et al., 2014). Given that an estimated 8.5% of Medicaid patients carry a schizophrenia diagnosis, efforts to increase integrated care management for such patients is greatly warranted (Boyd et al., 2010).

Community Care of North Carolina (CCNC) is an enhanced primary care case management program for Medicaid enrollees throughout the state of North Carolina. CCNC has already been successful at reducing unnecessary ED and hospital utilization for patients with schizophrenia through careful coordination with community-based infrastructure, and is continually working to improve care for these patients (Jackson et al., 2015). In this study, we evaluate the relationship between antipsychotic medication adherence and ED utilization among CCNC-enrolled Medicaid patients with schizophrenia.
2. Methods

2.1. Study design and population

This retrospective cohort study used available CCNC data for patients with schizophrenia enrolled in the program between January and December 2015. These data were taken from monthly reports derived from Medicaid claims and compiled by the CCNC behavioral health administrative team. They include the number of antipsychotic prescriptions each patient had filled in the past year, the number of medical and psychiatric ED visits and hospitalizations in the past year, and an array of demographic and clinical diagnosis variables.

For inclusion in the study, patients had to be between the ages of 18 and 65 at the start of the study, carry a diagnosis of schizophrenia or schizoaffective disorder (ICD-9-CM codes 295.0–295.9 documented on at least 2 Medicaid claims prior to the study period) and have been enrolled in CCNC prior to and continuously throughout the 12-month study period. To eliminate those patients who may carry a diagnosis of schizophrenia erroneously or who had never been prescribed antipsychotic therapy, patients were excluded if they did not have at least one antipsychotic fill in the 6 months prior to the study period and at least one fill during the study period. Patients receiving long-acting injectable antipsychotics were also excluded, given that these medications are typically prescribed due to a history of poor adherence and thus confound the relationship between adherence to oral antipsychotics and utilization. This study was reviewed by the Duke Health Institutional Review Board and found to be exempt, given that all data had been de-identified prior to the start of the study. Use of the data was approved by the North Carolina Division of Medical Assistance, the state’s Medicaid agency.

2.2. Measurement of variables

To estimate antipsychotic adherence, a modified medication possession ratio (MPR) was calculated for each patient using the following method: the total number of days of medication supply was estimated by the number of pharmacy fills during the study period, and then divided by the number of days in the fixed study period (365 days). Due to limitations in the de-identified data, it was not possible to determine the exact length of time covered by each pharmacy fill (e.g. 30-day versus 90-day). Because the large majority of CCNC patients receive standard 30-day prescriptions, one pharmacy fill approximated medication possession for 30 days. Additionally, the data was not able to specify which patients were being prescribed more than one antipsychotic. To address and simplify this issue, MP Rs ≥1 were truncated at 1. MPR ≥0.80 was defined as full adherence, consistent with prior literature (Lachaine et al., 2015; Lang et al., 2010; Rascati et al., 2011). To further characterize partial and non-adherence, five categories of the MPR were created (≤0.20, 0.20–0.40, 0.40–0.60, 0.60–0.80, ≥0.80).

The primary outcome variable was the number of ED visits in the study year—divided into psychiatric (behavioral health-related) and medical (non-behavioral health-related) ED visits. Visits were categorized as psychiatric or behavioral health-related if the encounter claim originated from a behavioral health managed care organization (all mental health-related encounters for Medicaid patients in North Carolina are routed through BH MCOs). Age and gender were included as covariates in the analyses. To control for medical comorbidity, a battery of diagnostic coding was transitioned from ICD-9 to ICD-10 in October 2015, facilitating disease (COPD), asthma, ischemic vascular disease, chronic gastrointestinal disease, and chronic neurologic disease. All variables in the regression were tested for multicollinearity by calculating variance inflation factors (VIFs). All VIFs were <2.

For the ED visit diagnoses, the numbers and percent of all ED visits in each of the 18 general disease groups were calculated. All analyses were performed using Stata® v.14.

2.3. Statistical analysis

Descriptive statistics were performed to demonstrate baseline characteristics for all patients in the study, stratified by adherence category. Categories were compared using Person’s chi-squared test. The mean number of psychiatric and medical ED visits was calculated for each adherence category. Analysis of variance (ANOVA) was used to compare means across categories.

To further explore the relationship between ED use and medication adherence, the incidence rate ratios of ED visits for patients in the partially adherent categories, compared to full adherence, was calculated. A negative binomial regression was used to calculate these ratios, given that the distribution of ED visits across patients approximated a negative binomial distribution. The regression was adjusted for age, gender, chronic disease variables, primary care use, and psychiatric and non-psychiatric hospitalizations, as described above. Disease variables were included in the final model if they were correlated with rates of ED visits and varied across categories of adherence. These included diabetes mellitus, hypertension, chronic obstructive pulmonary disease (COPD), asthma, ischemic vascular disease, chronic gastrointestinal disease, and chronic neurologic disease. All 295.9 documented on at least 2 Medicaid claims prior to the study period and have been enrolled in CCNC prior to and continuously throughout the 12-month study period. To eliminate those patients who may carry a diagnosis of schizophrenia erroneously or who had never been prescribed antipsychotic therapy, patients were excluded if they did not have at least one antipsychotic fill in the 6 months prior to the study period and at least one fill during the study period. Patients receiving long-acting injectable antipsychotics were also excluded, given that these medications are typically prescribed due to a history of poor adherence and thus confound the relationship between adherence to oral antipsychotics and utilization. This study was reviewed by the Duke Health Institutional Review Board and found to be exempt, given that all data had been de-identified prior to the start of the study. Use of the data was approved by the North Carolina Division of Medical Assistance, the state’s Medicaid agency.

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3. Results

3.1. Patient characteristics

A total of 7851 Medicaid patients enrolled in CCNC met criteria for inclusion in this study. Table 1 displays the patient characteristics. Patients had a mean age of 44.6 ± 12.4 years, and 52.2% were male. Rates of chronic diseases, particularly diabetes and hypertension, were quite high across patients. Seventy-five percent of all patients had visited a primary care provider, 12.8% had at least one medical hospitalization, and 8.2% had at least one psychiatric hospitalization during the study year. The mean MPR across all patients was 0.73 ± 0.30, and 4454 patients (56%) had an MPR ≥0.80. All variables except gender demonstrated a statistically significant difference across categories of medication adherence (chi-squared p-values < 0.05). Compared to fully adherent patients, partially or non-adherent patients were slightly younger, had less medical comorbidity, and had lower rates of primary
medical care. These patients were also more likely to have been hospitalized for either medical or psychiatric conditions.

3.2. Medication adherence and ED visits

Fig. 1 illustrates the relationship between medication adherence and ED utilization for both medical and psychiatric complaints. The study cohort had, on average, 11.31 times as many medical as psychiatric ED visits (means: 1.47 ± 3.67 vs 0.13 ± 0.59). Lower levels of adherence were strongly associated with more medical ED visits (F = 25.42, p \textless 0.001) whereas the association between adherence and psychiatric visits was much smaller (F = 3.87, p = 0.004).

The results of the negative binomial regression are displayed in Table 2. According to these results, non- or partially adherent patients (MPR < 0.80) had 1.61 (1.50–1.74) times the rate of medical ED visits as fully adherent patients (MPR \geq 0.80). For each category of partial adherence, the adjusted rate ratios followed a consistent, dose-response pattern—decreasing levels of adherence were associated with increasing rates of medical ED rates. The lowest level of adherence (MPR < 0.20) had 2.18 (1.92–2.47) times the rate of medical

Table 1
Baseline characteristics of CCNC patients with schizophrenia treated with oral antipsychotics, stratified by adherence to antipsychotics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 7851)</th>
<th>Adherence category (medication possession ratio)</th>
<th>p-Value\textsuperscript{d}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;0.20 (n = 748)</td>
<td>0.20—&lt;0.40 (n = 678)</td>
<td>0.40—&lt;0.60 (n = 970)</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>44.6 (12.4)</td>
<td>40.6 (12.4)</td>
<td>42.2 (12.7)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>3750 (47.8%)</td>
<td>350 (46.8%)</td>
<td>318 (47.5%)</td>
</tr>
<tr>
<td>Male</td>
<td>4101 (52.2%)</td>
<td>398 (53.2%)</td>
<td>352 (52.5%)</td>
</tr>
<tr>
<td>Chronic diseases:a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>2155 (27.4%)</td>
<td>129 (17.2%)</td>
<td>134 (20.0%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3631 (46.2%)</td>
<td>299 (40.0%)</td>
<td>265 (39.6%)</td>
</tr>
<tr>
<td>COPD</td>
<td>1115 (14.2%)</td>
<td>81 (10.8%)</td>
<td>90 (13.4%)</td>
</tr>
<tr>
<td>Asthma</td>
<td>1045 (13.3%)</td>
<td>121 (16.2%)</td>
<td>104 (15.5%)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>524 (6.7%)</td>
<td>50 (6.7%)</td>
<td>40 (6.0%)</td>
</tr>
<tr>
<td>Chronic gastrointestinal disease</td>
<td>1751 (22.3%)</td>
<td>152 (20.3%)</td>
<td>123 (18.4%)</td>
</tr>
<tr>
<td>Chronic neurologic disease</td>
<td>853 (11.4%)</td>
<td>88 (11.8%)</td>
<td>55 (8.2%)</td>
</tr>
<tr>
<td>Use of primary careb</td>
<td>5864 (74.7%)</td>
<td>476 (63.6%)</td>
<td>468 (69.9%)</td>
</tr>
<tr>
<td>Medical hospitalizationc</td>
<td>1006 (12.8%)</td>
<td>109 (14.6%)</td>
<td>89 (13.3%)</td>
</tr>
<tr>
<td>Psychiatric hospitalizationc</td>
<td>642 (8.2%)</td>
<td>106 (14.2%)</td>
<td>59 (8.8%)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Percent of patients with indicated chronic disease.
\textsuperscript{b} Number of patients with at least 1 primary care visit during 1-year study period.
\textsuperscript{c} Number of patient with at least 1 hospitalization during 1-year study period.
\textsuperscript{d} p-Values for Person's chi-squared test.

\[0.18\quad 0.14\quad 0.17\quad 0.13\quad 0.11\]

**Fig. 1.** Mean number of psychiatric and medical ED visits, stratified by categories of antipsychotic adherence (medication possession ratio). ANOVA for difference in means: psychiatric visits F = 3.87, p-value = 0.004; medical visits F = 25.42, p-value < 0.001.

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ED visits as fully adherent patients. Rate ratios for psychiatric visits were small. Only the category of MPR 0.40–0.60 demonstrated statistical significance at the 95% level (rate ratio 1.30, CI: 1.01–1.68, p-value = 0.046). The results of sensitivity analysis, excluding patients with medical or psychiatric hospitalizations, did not differ significantly from the original analysis (please see Supplementary material—Appendix 2).

3.3. ED diagnoses

Table 3 displays the major disease categories for all of the ED visit encounters from our study population during the study period. The leading cause of ED visits was injuries and poisonings (16.0%). This included a wide array of sprains, strains, superficial injuries, lacerations, and medication overdoses. This was followed by ill-defined symptoms and conditions (13.5%), which predominantly included conditions such as non-specific abdominal pain, nausea and vomiting, and syncope. Musculoskeletal and connective tissue disorders constituted the third leading cause (11.4%), which predominantly included back pain, intervertebral disc disorders, and other joint disorders. Fourth was neurologic diseases and conditions of the eyes and ears (11.3%), including headaches, seizures, neuropathies and neuralgias, vertigo, balance problems, and visual disturbances.

Table 3

Leading disease groups for ED visits among patients in study cohort during 1-year study period.

<table>
<thead>
<tr>
<th>Disease groupa</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injury and poisoning</td>
<td>2223</td>
<td>16.0</td>
</tr>
<tr>
<td>Ill-defined symptoms and conditions; factors influencing health care</td>
<td>1868</td>
<td>13.5</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>1579</td>
<td>11.4</td>
</tr>
<tr>
<td>Neurologic, eye, and ear diseases</td>
<td>1565</td>
<td>11.3</td>
</tr>
<tr>
<td>Respiratory diseases</td>
<td>1535</td>
<td>11.1</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>1198</td>
<td>8.6</td>
</tr>
<tr>
<td>Digestive diseases</td>
<td>908</td>
<td>6.6</td>
</tr>
<tr>
<td>Genitourinary diseases</td>
<td>844</td>
<td>6.1</td>
</tr>
<tr>
<td>Mental illness</td>
<td>545</td>
<td>3.9</td>
</tr>
<tr>
<td>Diseases of the skin and subcutaneous tissue</td>
<td>485</td>
<td>3.5</td>
</tr>
<tr>
<td>Endocrine; nutritional; and metabolic disorders</td>
<td>319</td>
<td>2.3</td>
</tr>
<tr>
<td>Residual codes; unclassified</td>
<td>317</td>
<td>2.3</td>
</tr>
<tr>
<td>Diseases of the blood/blood-forming organs</td>
<td>207</td>
<td>1.5</td>
</tr>
<tr>
<td>Infectious and parasitic diseases</td>
<td>158</td>
<td>1.1</td>
</tr>
<tr>
<td>Complications of pregnancy and childbirth</td>
<td>93</td>
<td>0.7</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>16</td>
<td>0.1</td>
</tr>
<tr>
<td>Congenital anomalies</td>
<td>2</td>
<td>0.0</td>
</tr>
<tr>
<td>Total</td>
<td>13,862</td>
<td>100</td>
</tr>
</tbody>
</table>

a Primary diagnosis for each ED visit, classified according to AHRQ Multilevel Clinical Classification Software.

4. Discussion

This study examines the relationship between antipsychotic medication adherence and emergency department utilization among Medicaid patients with schizophrenia. Interestingly, this study found that the overwhelming majority of ED utilization among patients with schizophrenia is categorized as medical rather than psychiatric, and that partial and non-adherence to antipsychotics are associated with increased ED utilization for medical conditions, but not necessarily psychiatric conditions. In general, the less adherent patients were, the higher their rate of medical ED use.

There are multiple possible explanations for this interesting observation. First, non-adherent or partially adherent patients may present to the emergency department with symptoms and conditions related to poorly controlled schizophrenia; their visits, however, are codified as a medical primary diagnosis. This phenomenon has not been extensively studied but is plausible given the high prevalence of somatization among patients with schizophrenia (Ritsner, 2003) and the high potential for misclassification of symptoms in a fast-paced emergency setting. The leading disease groups we identified—including injury/poisonings, ill-defined symptoms and conditions, and musculoskeletal/neurologic conditions—all have the potential for significant psychiatric overlap. Indeed, a proportion of the injuries/poisonings may actually represent medical conditions that are a direct result of uncontrolled psychiatric conditions (e.g. suicide attempts, injuries as a result of disorganized behavior, drug/alcohol intoxication, etc.) Unfortunately, limitations in the data and the way in which visits are coded do not allow us to further explore this possibility.

Second, non-adherence or partial adherence is associated with poorer self-care and medical follow-up, and this may lead to increased ED utilization for medical conditions (Hansen, 2012). It is well-known that patients with schizophrenia are more likely to suffer from one or more chronic medical conditions than the general public, and are much less likely to receive adequate care for these conditions (Horvitz-Lennon et al., 2006; Institute of Medicine (US) Committee on Crossing the Quality Chasm: Adaptation to Mental Health and Addictive Disorders, 2006). Indeed, our study found that less-adherent patients were less likely to have seen a PCP in that past year, suggesting inadequate primary care follow-up for these patients. Additionally, prior research has shown that poor antipsychotic adherence is associated with poor adherence to medications for chronic cardiometabolic conditions (Hansen, 2012), which in turn may contribute to the increased ED utilization observed in this study. However, it is worth noting that the leading ED diagnoses identified in this study were not associated with chronic cardiovascular or metabolic conditions, but rather included injuries, poisonings, various nonspecific complaints, and musculoskeletal and neurologic conditions. Thus, cardiometabolic medication adherence offers, at best, only a partial explanation to the link between antipsychotic adherence and ED utilization. Future research should further explore this relationship.

The findings of this study contribute to our understanding of the complex interplay between medication adherence and health care utilization. The reasons for nonadherence among Medicaid patients with schizophrenia are multifaceted, and often not necessarily related to patient behavior or unwillingness to comply with treatment. Many patients experience gaps in adherence due to lack of access to a provider or prescription. Thus, better behavioral health care coordination can potentially have a significant impact on addressing medication adherence. Meeting the needs of high-cost Medicaid patients with high rates of acute-care use has become a priority for state governments and health systems (Billings and Mijanovich, 2007). This study identifies an important area of focus for management of high-cost patients with schizophrenia.

One significant limitation of this study is that it cannot establish a clear causal relationship between patient adherence and ED use due to its observational design and the risk of unobserved variable bias. Patients who are more ill with various medical conditions may be more likely to use the emergency department and less likely to adhere to...
medications. We have reduced the risk of this bias by controlling for medical comorbidity. However, we are unable to control for the severity of schizophrenia across patients and how this may influence both adherence and ED utilization. Additionally, various social factors not captured in our data—such as homelessness, substance abuse, and lack of social support—are also likely to affect both ED utilization and medication adherence. Patients in more unstable socioeconomic circumstances are less likely to be adherent to medications and are more likely to frequent the emergency department (Lin et al., 2015; Phan, 2016). Exploring the complex interaction of social factors with medication adherence and ED utilization was beyond the scope of this study. However, it is a very important consideration in continuing research on the link between adherence and healthcare utilization in patients with schizophrenia.

Another limitation is that this study is unable to capture the temporal relationship between non-adherence and ED use, given the available data. That is, we are not able to show whether specific periods of non-adherence correspond to greater ED use during that same period. Such analysis would provide greater evidence for causality. In the literature that explores non-adherence and hospital utilization, many have raised the concern of reverse causality—more hospitalizations lead to greater non-adherence because patients do not fill prescriptions during long periods of hospitalization (Jiang and Ni, 2015; Weiden et al., 2004). Our analysis did not include inpatient encounters, nor did we have access to data on the antipsychotic medications administered to patients during psychiatric or medical hospitalizations. However, our sensitivity analysis in which we eliminated all patients who had at least one psychiatric or medical hospitalization during the study period did not show any statistically significant difference from the original analyses, suggesting that even if this reverse causality exists, it does not pose a threat to the validity of our results.

Lastly, the medication possession ratio is an imperfect measure of medication adherence. It does not give information as to whether a patient actually took the medication as prescribed, nor does it show whether patients were consistent in their adherence across the study period. It is very likely that full adherence, as measured by medication possession, does not necessarily translate into full adherence in reality. However, in the absence of more effective methods for monitoring medication use, the MPR is the best approximation of adherence available.

5. Conclusions

This study demonstrates a clear association between antipsychotic use and ED utilization, highlighting the importance of antipsychotic medication adherence in patients with schizophrenia. From a population health standpoint, it also highlights the important link between behavioral health care and medical utilization among Medicaid patients with schizophrenia. More research is needed understand the causes for non-adherence among Medicaid patients with schizophrenia, as well as the best methods for improving adherence.

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Conflicts of interests
Morgan Hardy—none.
Carlos Jackson—none.
Jennie Byrne—none.

Contributors
Morgan Hardy conducted all of the analyses and wrote the manuscript. Carlos Jackson procured the data, developed the concept for the study, provided statistical expertise, and edited the manuscript. Jennie Byrne served as a research mentor to Morgan Hardy, helped develop the concept of the study, edited the manuscript, and provided logistical support. All authors contributed to and have approved the final manuscript.

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References