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Associations Between Patient Characteristics and Utilization in a Commercial Schizophrenia Population

Thomas Joseph Bunz
University of Rhode Island, thomasbunz@gmail.com

ASSOCIATIONS BETWEEN PATIENT CHARACTERISTICS AND UTILIZATION IN A COMMERCIAL SCHIZOPHRENIA POPULATION

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THOMAS JOSEPH BUNZ

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THOMAS JOSEPH BUNZ

APPROVED:

Dissertation Committee:

Major Professor: Stephen Kogut, Ph.D.

E. Paul Larrat, Ph.D.

Brian Quilliam, Ph.D.

Marlene Dufault, Ph.D.

Nasser H. Zawia, Ph.D.

DEAN OF THE GRADUATE SCHOOL

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Abstract:

Background: Schizophrenia is a prevalent and costly condition in the United States. Many studies have been conducted on the schizophrenia populations receiving government sponsored insurance, but less is known about the 16% of the population that receives commercial insurance. A better understanding of the utilization and outcomes in this population is essential to ensure that outreach programs target the groups most in need, that these programs are aimed at the most important aspects of utilization, and that those factors are tied to meaningful clinical outcomes.

Objectives: The purpose of this research has been to better understand the patient characteristics, utilization patterns, and outcomes in patients with schizophrenia that participate in commercial insurance plans. Three studies have been completed to address the following specific aims: 1) To describe the schizophrenia population, 2) To determine if the sociodemographic, clinical, and employment characteristics of these patients are associated with their utilization patterns, and 3) To determine if adherence to therapy is associated with the rate of hospitalization for mental health conditions.

Methods: In order to accomplish these goals several studies have been completed utilizing claims data from calendar years 2000 and 2001. The first is a retrospective cohort analysis identifying relationships between utilization of first and second generation antipsychotics, switching between therapies, and combination therapy and patient characteristics; the second study identifies the associations between patient characteristics and adherence; the final study

utilizes a retrospective cohort design to determine the association between adherence and hospitalizations.

Results: Patient characteristics are a significant predictor of utilization, with individuals living in the North Central region and individuals with comorbid bipolar disorder significantly more likely to use second generation antipsychotics. Adherence was associated with comorbid diabetes and mental health disorders. Adherence as measured by an MPR greater than or equal to 80% was associated with a lower risk of hospitalization due to mental health conditions.

Conclusion: This series of studies has identified significant associations between comorbidities and increased likelihood to switch medications, utilize a second generation antipsychotic, or combine therapies. Comorbidities also increase the likelihood that someone will not be adherent to their therapy. Low adherence to therapy in turn increases the likelihood of hospitalization.

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Preface

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CHAPTER 1

ANALYSIS OF THE DEMOGRAPHIC, EMPLOYMENT, AND CLINICAL CHARACTERISTICS OF ANTIPSYCHOTIC UTILIZERS IN A COMMERCIALLY INSURED POPULATION

Formatted for submission to the Journal of Managed Care Pharmacy (JMCP), not yet submitted.

Abstract:

Background

Schizophrenia is a difficult and expensive condition to treat. In the United States, many individuals with this condition are managed by federal health insurance programs, as a result most database studies examine schizophrenia treatment at the VA, or in Medicare and Medicaid populations. The purpose of this analysis is to better understand treatment patterns in the commercial population, where 16% of the schizophrenia population is managed.

Methods

A retrospective cohort study was conducted utilizing data from the Thomson Marketscan database between January 1, 2000 and December 31, 2001. Individuals with schizophrenia were identified based on documentation of an ICD-9 (295.xx) code during year one. Three logistic regression models were then used to determine if there was an association between first and second generation antipsychotic use, switching, and combination of therapies; and demographic, clinical, and employment characteristics of the population.

Results

Second generation antipsychotic use was associated with living in the North Central area of the United States (OR 1.3, 95% CI 1.053 - 1.603), comorbid bipolar disorder (OR 1.271, 95% CI 1.072 - 1.507), and switching (OR 1.937, 95% CI 1.568 - 2.393). Individuals who switched therapy were nearly twice as likely to have been taking a first generation antipsychotic before the switch (OR 1.962, 95% CI 1.583 - 2.431) Combination therapies were less likely in the North

Central (0.727, 95% CI 0.554 - 0.955) and Southern (0.534, 95% CI 0.411 - 0.694) regions as compared to the North East.

Conclusion

There were significant associations between certain demographic, clinical, and employment characteristics and the antipsychotic therapies received by individuals in the commercial population.

Background:

Prevalence

Mental health disorders are prevalent in the United States, and treating these conditions can be difficult and expensive. A study conducted by Kessler et al, found that the lifetime prevalence of schizophrenia for adults in the United States is between 0.3% and 1.6%.[1] A systematic review of the literature found that the period prevalence of schizophrenia is between 0.13% and 0.82%.[2] An evaluation of a commercially insured population found that the prevalence of schizophrenia in that group is near the lower end of the range, at about 0.13%.[3] Despite being less prevalent in the commercial population, people in this group make up a significant portion (16%) of the schizophrenic population.[3]

Treatment Decisions

Finding an appropriate treatment for schizophrenia is difficult. It can take up to sixteen weeks to see the positive effects of treatment,[4] and even with effective treatment the negative symptoms of schizophrenia (such as social and emotional withdrawal, poor rapport, and blunted affect) are still common.[5] As a result, roughly 74% of patients are expected to discontinue treatment during the first 18 months.[6] In addition to difficulty finding and adjusting to a treatment, the adverse events associated with both first and second generation antipsychotics are associated with lower adherence.[7] In first generation antipsychotics, the

extrapyramidal side effects were closely associated with discontinuation, while metabolic effects lowered adherence in users of Second Generation Antipsychotics,[6,8] A study by Staring, et al, found that high adherence was associated with decreased quality of life, as was low adherence due to the balance of symptoms and adverse events.[9] It has become clear that adequate treatment with antipsychotics will lower the mortality rate in the schizophrenia population,[10] but there are also associations between antipsychotics and increased cardiovascular mortality that have yet to be fully understood.[11]

There are several studies that have tried to define the best strategy for selecting an initial antipsychotic. The CATIE and CutLASS studies were prospective open label trials, but the treatments included for study, population characteristics, and study limitations have limited the acceptance of their findings by clinicians.[12] Several studies have provided support for the use of First Generation Antipsychotics. In a Medicare population, Second Generation Antipsychotic users were significantly more likely to be hospitalized as compared to non-users, while First Generation Antipsychotic users had roughly the same hospitalization rate as non-users.[13] CATIE found that users of perphenazine saved roughly $300-600 over users of Second Generation Antipsychotics.[14] Amongst Second Generation Antipsychotics, a review of the literature found no clear benefit to any one choice.[15] Despite the limited support in the literature, and no preference in treatment guidelines, there has been a major shift in use of antipsychotics from the first to second generation agents.[16] Race, age, and

comorbidities were all factors closely associated with the decision to use a second generation antipsychotic in a Veteran population.[16]

The population utilizing antipsychotics is not limited to individuals with schizophrenia. In an analysis of a Veterans population, 60.2% of the population had no indication of a schizophrenia or bipolar diagnosis.[17] The most common off label use in this population was Post Traumatic Stress Disorder (PTSD) (about 40% of the population had this diagnosis). In a Medicaid population in Oregon, only 15% of patients receiving had a documented diagnosis of schizophrenia.[18]

In addition to adverse events, comorbidities complicate the treatment of schizophrenia. It has been found that despite physician knowledge of the problem, schizophrenic patients still do not receive appropriate treatments for their comorbid conditions.[19] Patients with these conditions are often diagnosed with both mental health and general health issues, with one of the most common in schizophrenics being bipolar disorder.[20] In schizophrenia, comorbid depression is closely linked to relapses,[21] and anxiety is diagnosed in roughly 60% of the population.[22] The major general comorbidities driving treatment decisions are diabetes and cardiovascular disease.[23, 24] Diabetes occurs in 10.3% of schizophrenics, as compared to 5.6% of the general population.[25] In the schizophrenic population, these increased risks are associated with greater risk of death from comorbidities,[26] and a nursing home admission rate in 40-64 year olds that is 3.9 times higher than the general population.[27]

Switching and Combinations

Switching between antipsychotics is a fairly common practice. The CATIE trial found that in the best case scenario, 36% of patients taking olanzapine remained on treatment at 18 months. Only 17% of quetiapine patients, 26% of risperidone patients, and 20% of ziprasidone patients remained on these second generation antipsychotics at 18 months. Perphenazine represented first generation antipsychotics in this trial, and 25% of patients remained persistent at 18 months.[14] In almost all cases patients switched to a second generation antipsychotic, in only 1.2% of treatment episodes did an individual move from second generation to first generation. An earlier study by Menzin, et al, found that 58% of first generation antipsychotic users switched to another antipsychotic (most often a second generation antipsychotic) while only 33% of second generation antipsychotic users switched to another antipsychotic (also most often a new second generation antipsychotic).[28]

The use of combination therapy is highly controversial. The practice has been observed in between 5% and 18% of the population according to a review of the literature.[4] There is scant evidence that polypharmacy results in better outcomes for individuals,[4] although patients taking multiple medications do demonstrate poorer adherence.[29] The most common combinations seen in database analyses involve two second generation antipsychotics, or a first and a second generation medication.[30] The Joint Commission for Quality Improvement has laid out a set of narrow guidelines where combinations of two or more

antipsychotics might be reasonable, such as in patients utilizing Clozapine, multiple failed trials of monotherapy, or if discharged from a hospitalization with two or more medications.[31]

Study Purpose and Justification

There have been many studies conducted to better understand the populations utilizing antipsychotics. The vast majority of the literature identified above focuses on specific populations with a high incidence of schizophrenia, those individuals utilizing Medicaid and VA programs. The commercial population likely differs significantly from the Medicaid and VA groups where patients are typically older, and (especially in the VA) more likely to be male.[16, 28] This population is also different from the CATIE population, in which 85% of the population was unemployed.[6] A better understanding of how antipsychotic medications are utilized within commercial populations is critical. Sixteen percent of schizophrenics receive services through private insurance.[3] Programs designed to better manage these populations will utilize the improved information to better understand their participants.[32, 33]

The goal of this analysis is to describe the primary medication taking characteristics of commercially insured patients utilizing antipsychotic medications; these characteristics are: the use of first or second generation agents, switching treatments, and combination of treatments. These

characteristics will be examined in relationship to the demographic, clinical, and employment characteristics of the patients.

Methods:

Study Design:

A retrospective cohort study was conducted utilizing the Thompson MarketScan database. Those individuals utilizing antipsychotic medications, and diagnosed with schizophrenia were identified. The primary treatment outcomes studied were choice of first or second generation antipsychotic, switching of treatments, and use of combination treatment. Associations between these outcomes and the demographic, clinical, and employment characteristics of the populations were assessed.

Data:

Data for this analysis was made available through the Thomson Medstat dissertation support program. This program provides access to de-identified data in the MarketScan database from years 2000 and 2001. This database contains enrollment and demographics data, as well as medical and pharmacy claims for nearly 5.9 million individuals, including employees and their dependents working for large companies spread across the United States, and insured by roughly 100 different payers.

Inclusion Criteria:

Continuous enrollment is a key criterion for inclusion in this analysis. Although this requirement narrows the study population significantly, it is essential to ensure that key events such as prescription dispensings and encounters with medical professionals are recorded in the database, and available for the description of the population. Individuals over 65 years of age during the study period were also excluded from the study population in order to avoid biases resulting from missing data associated with the coordination of benefits between Medicare and commercial insurers. Individuals under the age of 18 were excluded in order to avoid similar benefit coordination issues in a pediatric environment. Patients also had to have at least one diagnosis code indicating schizophrenia during the 2 year study period (Table I-1).

Operational Definitions:

Continuous enrollment was defined as having 366 days of continuous enrollment in 2000, and 365 days of continuous enrollment in 2001 with both medical and pharmacy coverage. This data was abstracted from the enrollment data sets provided.

Diagnoses for specific conditions were identified through the presence of one or more ICD-9 codes in the inpatient or outpatient records between January 1, 2000 and December 31, 2001. Anxiety, Bipolar Disorder, Depression,

Schizophrenia, Other Mental Health Disorders not included above, and Diabetes were all identified. The specific list of ICD-9 codes used to identify these conditions is provided in table I-1. This methodology is similar to that used in a variety of other studies,[3, 34-36] and validated by Rawson, et al, in 1997.[36]

A treatment episode with a given therapy was defined as receipt of at least 2 dispensings on different days within the study period. Individuals with no treatment episodes were excluded from the bivariate and multivariate analyses. Therapies were defined as a "new treatment" if there was no record of that treatment being received during the six months preceding the first fills. The "therapeutic period" for a treatment was defined as the time from the first fill, to the date of the last fill plus the last days supply. "Combination Therapy" was defined as two treatments overlapping by a minimum of 90 consecutive days. A "switch" in therapy is defined as a change from one treatment to another where there is no more than a 90 day gap in therapy, and no more than 90 days of overlap in therapy. A "gap" in treatment is defined as a period of 90 days or more following the end of a therapeutic period. Studies have typically used periods of 30 to 90 days to define gaps in therapy.[34, 35, 37] This study utilized the 90 day period to match the longest days supply routinely received by patients.

Demographic variables were examined for missing or obviously erroneous data through examination of distributions and outliers. An individual's age was defined as the difference between their birth year, and the year 2000. There were no instances in the data where an individual had more than 1 gender on record. Descriptions of employment type (primary vs. secondary policy holder,

full time vs. part time, and hourly vs. salaried) and geographic variables were defined for each individual as the value that turned up most often for that individual (if more than one value was available).

Bivariate Statistical Analysis:

Bivariate analyses were conducted in order to determine the associations between the three outcomes (antipsychotic generation choice, switching, and combination use) and the demographic, clinical, and employment variables. The students t-test was utilized for age, the only normally distributed continuous variable. Chi-square analysis was conducted for the binomial and categorical variables.

Multivariate Statistical Analysis:

Because of the potential for strong relationships between many of the explanatory variables explored in the bivariate statistical analysis, logistic regression was also used in each of the populations to examine the following:

1. Factors associated with the decision to use a second generation antipsychotic or a first generation antipsychotic
2. Factors associated with switching
3. Factors associated with combination use

The dependent variables tested were: type of antipsychotic, switch, and combination. The independent variables included in each model were: age, gender, region, rural / urban, full time employment, employee or dependent,

industry, and comorbidies (schizophrenia, bipolar disorder, depression, anxiety, other mental health, and diabetes). Variables were included in the model if they were found to be associated with the outcome variable in bivariate testing ($p < 0.2$). The exceptions are age and gender, which were included regardless due to their importance in understanding the make-up of the population. Interaction terms including the various combinations of age group, gender, and comorbidities were also included if they were associated with the dependent variable as measured by the chi-square test with a significant p-value (<0.2). Chi-square analysis was also used to assess several potential associations amongst independent variables to determine if they were independent. If the variables were not independent (chi-square value was less than 0.05), the less important variable was dropped from consideration for the model. Stepwise backwards elimination was used to optimize the model, using the -2 log likelihood to test the significance of changes. Multicollinearity was assessed based on the variation inflation factor (VIF), and eignevalues. These were calculated utilizing a separate model with the proc reg function in SAS with the VIF, TOL, and collin options. Hosmer-Lemeshow was used to assess goodness of fit.

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Results:

Study Population

A diagnosis for schizophrenia was recorded for 2,156 individuals (0.15% of the eligible population) between 2000 and 2001; table I-2 describes their demographic characteristics. Of the 2,156, a total of 1,517 (70.4%) received at least 2 dispensings for the same antipsychotic. Figure I-1 describes the population waterfall. A majority of this population was female (N=1,244 [57.7%]). The biggest group of schizophrenic patients lived in the south (43.7%), with 27.1% in North Central, 24.7% in the North East, and the remaining 4.4% in the West. 19.3% of the population lived in a rural setting. This reflects the general distribution of the population in the database. Of the population eligible for inclusion in this study, 0.15% had one or more documented ICD-9 codes indicating schizophrenia.

A majority of this population (56.3%) were active full time employees. Manufacturing was the most common known industry, with 32.0% (N=690) of individuals employed. Approximately half of the individuals in this population were spouses or dependents (1098 [50.9%]). There were more hourly workers than salary workers in this population (N=593 and 470 respectively). Details regarding employment in this population are in table I-2.

Comorbid conditions are described in table I-2. Bipolar disorder was identified in 29% (N=637) of this population, depression was documented in 489 (22.7%) individuals, and anxiety was documented in 245 (11.4%). Other mental

health disorders not listed above were identified in claims for 1,181 (54.8%) people. Diabetes was documented in 355 (16.5%) of individuals identified in this group.

There were 3,239 individual treatment episodes for antipsychotics in the schizophrenic population (table I-3), which averages to 1.5 per patient or 2.1 for each patient that used at least 2 fills of an antipsychotic. Second generation antipsychotics were utilized by 56.2% (N=1212) of the population, and first generation antipsychotics are used by 27.4% (N=591) of the schizophrenic population identified. Records indicating 2 or more dispensings of an antipsychotic are absent in 29.6% (N=639) of the population with documentation of schizophrenia, indicating that they are either untreated during this study period, or are receiving treatment through a source that is not recorded in the claims. The most commonly received antipsychotics were olanzapine and risperidone (received by 27.1% and 25.2% of the population respectively), table I-3 describes the rate of use for the remaining treatments.

Switching between one or more antipsychotics occurred prior to 21.7% (N=702) of the treatment episodes (in 13.6% of the population), while combination therapy was observed in 421 (13.0%) treatment episodes (in 12.9% of the population). The most common switches were between second generation antipsychotics. Table I-4 demonstrates the switches identified in the antipsychotic users. The majority of combinations were with first and second generation antipsychotics (N=262), with combinations of two second generation

antipsychotics also common (N=136). Table I-5 demonstrates the combinations utilized by this population.

Bivariate Analysis

First generation antipsychotic users were on average 3.1 years older than those using second generation antipsychotics in this population (table I-6), and 3.6% more individuals in the North East received a first generation antipsychotic than individuals living elsewhere; 9.2% more individual patients diagnosed with comorbid bipolar disorder received a second generation antipsychotic than those who were not diagnosed. After switching medications, the frequency of second generation antipsychotic use was 14.5% higher than if they were treatment naïve or starting on a therapy after a long gap.

Patients switching medications were on average, younger than those who did not switch, although there was no difference in age for those using combination treatments. Table I-7 describes associations with switching and combination use in this population. Patients with bipolar disorder in addition to schizophrenia were more likely to switch medications ($p<0.0001$). Those with anxiety were more likely to switch ($p<0.001$), but less likely to use combinations ($p= 0.004$). Type of employment was not associated with the rate of switching.

Multivariate Analysis:

In this population antipsychotic type was modeled against age, gender, region, comorbid diagnoses (bipolar disorder, depression, anxiety, and diabetes), switching, combination use, and employment variables for the full model. Salary, full time employment, combinations, and anxiety and depression diagnoses did not contribute significantly to the model (see table I-8). The final model had a reasonable goodness-of-fit with c=0.839, and the Hosmer-Lemeshow p-value of 0.353. The model indicated that as compared with residents of the North East region, individuals in the North Central region were more likely to receive a second generation antipsychotic (OR 1.3, 95% CI 1.053 – 1.603). In this population, individuals with a comorbid diagnosis of bipolar disorder were 27.1% (OR 1.271, 95% CI 1.072% – 1.507%), and individuals with other mental health conditions were 48.9% (OR 1.489, 95% CI 1.266 - 1.750) more likely to receive a second generation antipsychotic as compared with patients without the condition. Individuals who had switched from another medication were nearly twice as likely as those who had not switched to receive a second generation antipsychotic (OR 1.937, 95% CI 1.568 – 2.393). Age, gender, and comorbid diabetes were not significant (table I-9).

Switching therapy was modeled against age, gender, region, diagnoses, use of a second generation antipsychotic, combination use, and responsibility for insurance coverage. Responsibility for coverage was removed in the final model due to lack of significance (table I-8). This had a reasonable goodness-of-fit with

c=0.848, and the Hosmer-Lemeshow p-value of 0.275. Prior to switching, individuals were nearly twice as likely to have received first generation antipsychotics, as compared to a second generation antipsychotic (OR1.929, 95% CI 1.561 – 2.384) (table I-10). Individuals with comorbid bipolar disorder were 39% (OR 1.393 95% CI 1.163 – 1.668) more likely than those without a bipolar diagnosis to switch antipsychotics.

Use of combinations of treatments in the schizophrenia population was modeled against age, gender, rural location, region, diagnoses, use of a second generation antipsychotic, switching, and employment variables. Rural location, use of a second generation antipsychotic, and diagnoses besides anxiety were removed from the model because they did not make a significant contribution to the model (table I-8). The model had a good fit with c=0.895, and the Hosmer-Lemeshow p-value = 0.926. Individuals in the North East were more likely to receive medications in combination as compared with patients in the North Central and South regions (table I-11). Full time workers (OR 0.653, 95% CI 0.523 - 0.989), and those listed as primary on their insurance coverage (OR 0.785, 95% CI 0.623 - 0.815) were less likely than others to have combination therapies.

Discussion:

The results of this study draw some significant distinctions between the commercially insured and government insured populations receiving antipsychotic therapy for schizophrenia. Understanding these differences will improve the ability of the commercial managed care organizations to direct resources and focus on ensuring appropriate care for those individuals most likely to be switching or combining therapy, and help to ensure that those prescribing decisions are appropriate. The ability to do this could lead to improved quality of care and lower overall costs for both the payors and patients.

Utilization of First vs. Second Generation Antipsychotics

Age was a significant predictor of medication choice, with older individuals more likely to receive first generation antipsychotics than younger patients. One other study was identified that has used claims data to identify factors associated with utilization of antipsychotics. The association between older age and lower frequency of second generation antipsychotic use was similar to that identified in a Texas Veteran's population by Yang, et al.[16] In agreement with our findings Yang et al reported that patients having a documented diagnosis of bipolar disorder or other mental health disorders had an increased likelihood of receiving a second generation antipsychotic. However, the Yang et al study did not assess

the influence of a diagnosis of diabetes, region, or switching between medications.

The differences identified in prescribing by region between the North East and North Central areas of the country are supported by a variety of literature describing differences in medical costs and quality throughout the United States. Some of the most described examples of this are the regional differences in cost and quality in Medicare. Zhang et al found that in the South East there are significantly higher rates (up to 44%) of potentially inappropriate prescribing to the elderly, compared to New England where the highest rates observed were below 21%.[38]

Switching Rates

Individuals can switch between antipsychotics for a variety of reasons, including adverse events, lack of effectiveness, or concerns about cost. Although patients are commonly more adherent to treatment after a switch, there are potential adverse events associated with switching, especially if patients do not titrate propperly.[39] The results of this study are useful in establishing a baseline switch rate for individuals in a commercial population.

The likelihood of having switched therapies was twice as high among those individuals currently using second generation antipsychotics, and roughly 40% higher in those with bipolar disorder or depression. Age and gender were not significant influences on medication switching. Although having a comorbid

diagnosis of diabetes was associated with increased use of first generation antipsychotics, those with diabetes were also 34.5% more likely to switch medications. The increased rate of switching makes sense in those individuals with a more complex clinical situation due to the increased likelihood of adverse events and poorer adherence leading to inadequate outcomes,[28] and these trends are also supported by literature evaluating a Medicaid population.[28, 39] The rate of switching from first generation antipsychotics to second generation antipsychotics was also similar to that seen in the CATIE trial, which found that 18% of patients switched medications during an 18 month time period.[14]

Use of combination therapy

The frequency of combinations between first generation antipsychotics and second generation antipsychotics, as well as multiple second generation antipsychotics seen in our population was similar to that seen in the literature.[30] The overall combination rate of 12.9% was in the range identified in a review by Stahl, et al, which was 5-18% of all users of these medications within outpatient populations.[4] Combination therapy was significantly less common in individuals working full time, or currently responsible for providing insurance coverage. These factors are likely to be closely associated with disease severity, although given the short time period studied, it cannot be determined whether they simply are better responders to monotherapy, or if this group has a less severe underlying condition overall. Generally, the existing literature does not support

the utilization of polypharmacy, due to a lack of improved outcomes, increased adverse events, and higher costs,[4] although there are narrow circumstances in which combining multiple medications may be necessary and acceptable, such as after failure to respond in 3 or more trials of monotherapy, individuals using Clozapine, and those released from inpatient treatment with combination therapy.[31]

Combination therapy was also less common in individuals living in the North Central and Southern regions as compared to the North East. Further study is needed to understand why these regional differences exist, and no other studies conducted in the United States have been identified that address this discrepancy in therapy across regions. A Danish study identified regional differences in the understanding of clinical guidelines as one possible reason for differences in polypharmacy.[40]

Limitations

Although the goal of this analysis was to ensure generalizability to the commercially insured US population, the requirement of 2 years continuous data may have limited the inclusion of some of the more severe patients that were not enrolled for the entire study period. However, the proportion of schizophrenic individuals excluded from the study population due to our continuous enrollment requirement was smaller than the proportion of the overall population. Because the time available in the data set is relatively short, it was not possible to reliably

establish a temporal sequence, limiting the ability to understand the relationships between the observed factors and medication choice, switching, or combination use. The age of the data also limits generalizability due to the addition of new treatments and guidelines that may have subsequently changed practice over time.

This study is reliant on claims data submitted by physicians and pharmacies for the purposes of billing, therefore there are some limitations seen across retrospective database analyses. Pharmacy data indicating a medication is dispensed do not ensure that the medications are actually consumed, additionally individuals paying cash or receiving samples of their medication from their physician will not have records. Finally, diagnosis coding can be inaccurate, with some individuals with documentation of schizophrenia not having the condition, as well as the reverse, individuals diagnosed that do not have full documentation.

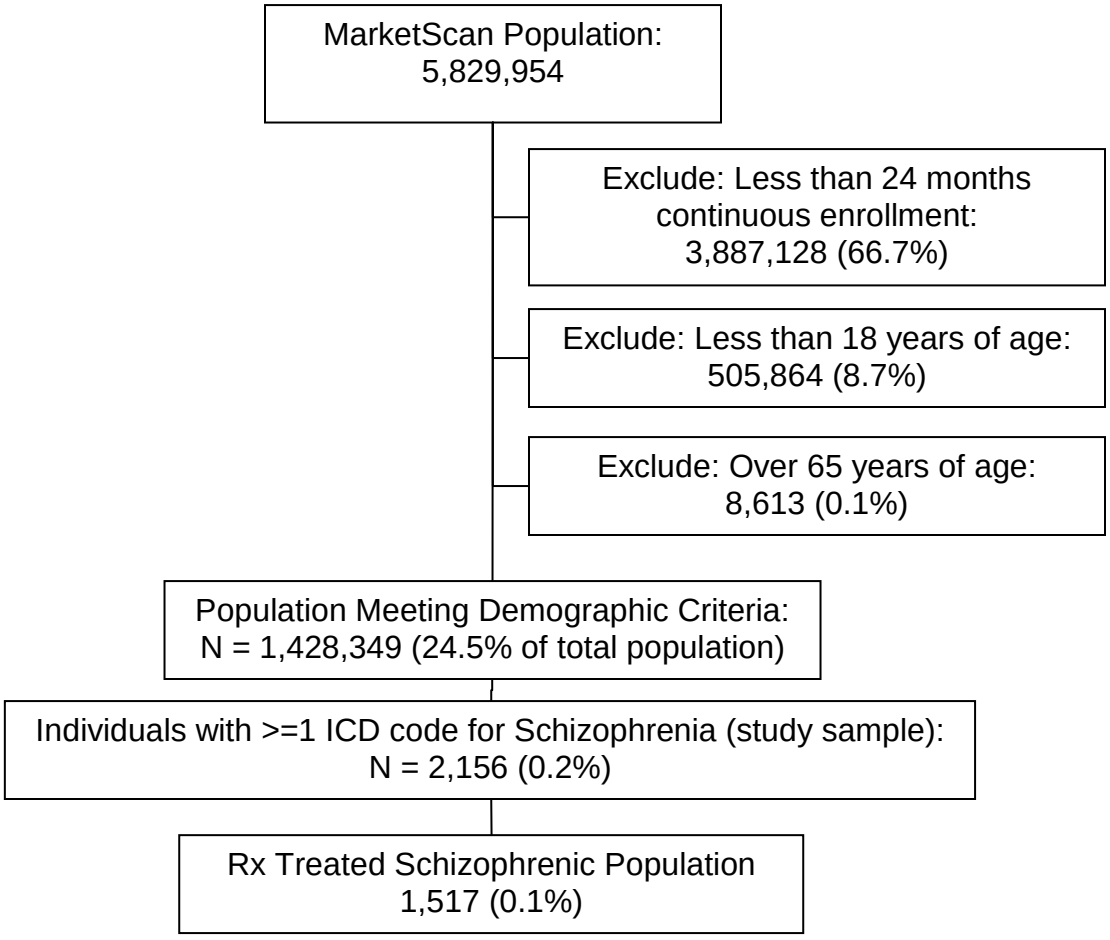
Smoking and obesity are confounders in the schizophrenia population that could not be addressed. Because of the metabolic side effects of second generation antipsychotics, obesity may have been an unobserved factor influencing an increased use of first generation antipsychotics. Smoking has been associated with lower adherence to medications,[41] but it is not clear whether it would impact combination therapy, switching, or the choice between first and second generation antipsychotics.

Conclusions

This analysis demonstrates the significant differences between a commercially insured schizophrenia population and the more commonly evaluated populations in federally insured programs. Comorbidities with diabetes and bipolar disorder were key drivers of increased therapy switches, while age and gender played a smaller role than that observed in other populations. Additional study is necessary to determine if these factors also impact an individual's ability to adhere to therapy.

Figures:

Figure I-1: Inclusion / Exclusion Criteria Flowchart



Tables:

Table I-1: ICD-9 Codes used for identifying diagnoses with primary conditions and comorbidities

Condition	ICD-9 Codes Included
Schizophrenia	295 - 295.95
Bipolar Disorder	296 - 296.99
Anxiety	300 - 300.09
Depression	311, 300.4
Other Mental Health	290 - 319, except for those listed above
Diabetes	250.00 – 250.99

Table I-2: Demographics of patients with a diagnosis for schizophrenia

			N / Mean	% / SD
Total Population N			2,156	100.0%
Demographic	Age	Mean (SD)	45.5	11.9
	Region	Northeast	533	24.7%
		North Central	584	27.1%
		South	942	43.7%
		West	95	4.4%
		Unknown	2	0.1%
Comorbidities	Mental Health Conditions	Bipolar	637	29.5%
		Depression	489	22.7%
		Anxiety	245	11.4%
		Other Mental Health	1,181	54.8%
	Others	Diabetes	355	16.5%
Employment	Employment Status	Active Full Time	1,213	56.3%
		Active Part Time or Seasonal	25	1.2%
		Early Retiree	800	37.1%
		Medicare Eligible Retiree	13	0.6%
		Retiree (status unknown)	34	1.6%
		COBRA Continuee	19	0.9%
		Long Term Disability	18	0.8%
		Surviving Spouse/Depend.	12	0.6%
		Other/Unknown	22	1.0%
	Industry	Oil & Gas Extraction, Mining	0	0.0%
		Manufacturing, Durable Goods	514	23.8%
		Manufacturing, Nondurable Goods	176	8.2%
		Transportation, Communications, Utilities	392	18.2%
		Finance, Insurance, Real Estate	43	2.0%
		Services	273	12.7%
		Unknown / Missing	758	35.2%
	Relationship to Employee	Employee	1,058	49.1%
		Spouse	708	32.8%
		Child/Other	390	18.1%
	Employment Class	Salary Non-union	146	6.8%
		Salary Union	166	7.7%
		Salary Other	158	7.3%
		Hourly Non-union	47	2.2%
		Hourly Union	171	7.9%
		Hourly Other	375	17.4%
		Non-union	175	8.1%
		Union	51	2.4%
		Unknown	857	39.7%

Table I-3: Frequency and percentage of the use of antipsychotic medication types within the study population

		N*	%
Total Population		2156	100.0%
No Treatment		639	29.6%
Second Generation	Any Second Generation	1212	56.2%
	Clozapine (Clozaril)	112	5.2%
	Ziprasidone (Geodon)	207	9.6%
	Risperidone (Risperdal)	544	25.2%
	Quetiapine (Seroquel)	294	13.6%
	Olanzapine (Zyprexa)	584	27.1%
First Generation	Any First Generation	591	27.4%
	Haloperidol (Haldol)	163	7.6%
	Loxapine (Loxitane)	35	1.6%
	Thioridazine (Mellaril)	61	2.8%
	Molindone (Mobane)	12	0.6%
	Thiothixene (Navane)	75	3.5%
	Pimozide (Orap)	3	0.1%
	Fluphenazine (Prolixin)	80	3.7%
	Mesoridazine (Serentil)	7	0.3%
	Trifluoperazine (Stelazine)	93	4.3%
	Chlorpromazine (Thorazine)	59	2.7%
	Perphenazine (Trilafon)	65	3.0%

*Total N does not sum due to use of combination therapies

Table I-4: Antipsychotic medication switches in the study population receiving more than one therapy

Swich From: / Switch To:	Clozapine (Clozaril)	Olanzapine (Zyprexa)	Quetiapine (Seroquel)	Risperidone (Risperdal)	Ziprasidone (Geodon)	Second Generation Antipsychotics	Chlorpromazine (Thorazine)	Droperidol (Inapsine)	Fluphenazine (Prolixin)	Haloperidol (Haldol)	Loxipine (Loxitane)	Mesoridazine (Serentil)	Molindone (Mobane)	Perphenazine (Trilafon)	Pimozide (Orap)	Thioridazine (Mellaril)	Thiothixene (Navane)	Trifluoperazine (Stelazine)	First Generation Antipsychotics
Clozapine (Clozaril)		4	8	6	2	20	1	0	1	1	1	0	0	1	0	0	3	0	8
Olanzapine (Zyprexa)	5		30	43	9	87	3	0	6	28	4	0	1	8	0	6	6	6	68
Quetiapine (Seroquel)	2	64		53	5	124	0	0	7	10	2	2	0	4	0	4	4	6	39
Risperidone (Risperdal)	5	49	25		4	83	9	0	11	23	1	0	0	2	1	6	7	5	65
Ziprasidone (Geodon)	2	24	7	27		60	2	0	4	3	0	0	0	2	0	2	2	2	17
Second Generation Antipsychotics	14	141	70	129	20	374	15	0	29	65	8	2	1	17	1	18	22	19	197
Chlorpromazine (Thorazine)	0	5	2	5	1	13		0	0	2	0	0	0	0	0	4	1	1	8
Droperidol (Inapsine)	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	0	0
Fluphenazine (Prolixin)	2	7	2	4	3	18	1	0		2	0	0	3	1	0	0	0	0	7
Haloperidol (Haldol)	0	11	7	15	2	35	1	0	2		1	0	0	1	0	0	1	0	6
Loxipine (Loxitane)	0	1	1	1	0	3	0	0	1	1		0	0	0	0	0	0	0	2
Mesoridazine (Serentil)	0	0	1	0	0	1	0	0	0	0	0		0	0	0	0	0	0	0
Molindone (Mobane)	0	0	1	0	1	2	0	0	0	0	0	0		0	0	0	0	0	0
Perphenazine (Trilafon)	0	1	2	2	0	5	0	0	0	0	0	0	0		0	0	0	1	1
Pimozide (Orap)	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	0	0	0
Thioridazine (Mellaril)	0	2	2	1	1	6	1	0	0	2	1	0	0	0	0		0	0	4
Thiothixene (Navane)	2	32	0	4	0	38	0	0	0	2	1	0	0	0	0	0		0	3
Trifluoperazine (Stelazine)	0	3	2	0	1	6	0	0	0	0	0	0	0	0	0	0	2		2
First Generation Antipsychotics	4	62	20	32	9	127	3	0	3	9	3	0	3	2	0	4	4	2	33

Table I-5: Antipsychotic medication combinations in the study population receiving more than one concomitant therapy

Drug 1 / Drug 2	Clozapine (Clozaril)	Olanzapine (Zyprexa)	Quetiapine (Seroquel)	Risperidone (Risperdal)	Ziprasidone (Geodon)	Second Generation Antipsychotics	Chlorpromazine (Thorazine)	Droperidol (Inapsine)	Fluphenazine (Prolixin)	Haloperidol (Haldol)	Loxipine (Loxitane)	Mesoridazine (Serentil)	Molindone (Mobane)	Perphenazine (Trilafon)	Pimozide (Orap)	Thioridazine (Mellaril)	Thiothixene (Navane)	Trifluoperazine (Stelazine)	First Generation Antipsychotics
Clozapine (Clozaril)		7	4	7	2	20	0	0	1	2	3	0	0	0	0	0	1	1	8
Olanzapine (Zyprexa)	3		15	15	11	44	1	0	10	19	2	0	2	4	0	4	0	3	45
Quetiapine (Seroquel)	3	8		10	4	25	2	0	6	9	0	0	1	8	0	1	3	4	34
Risperidone (Risperdal)	4	24	14		1	43	7	0	4	6	3	1	1	2	0	4	2	1	31
Ziprasidone (Geodon)	0	2	1	1		4	0	0	0	0	1	0	0	0	0	0	0	1	2
Second Generation Antipsychotics	10	41	34	33	18	136	10	0	21	36	9	1	4	14	0	9	6	10	120
Chlorpromazine (Thorazine)	0	6	1	3	0	10		0	1	0	0	0	0	1	0	0	0	3	5
Droperidol (Inapsine)	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	0	0
Fluphenazine (Prolixin)	0	10	8	4	0	22	1	0		0	0	0	0	0	0	0	0	0	1
Haloperidol (Haldol)	0	12	8	13	2	35	1	0	0		0	0	1	0	0	3	1	0	6
Loxipine (Loxitane)	0	0	4	0	1	5	0	0	1	0		0	0	0	0	0	0	0	1
Mesoridazine (Serentil)	0	1	1	0	0	2	0	0	0	0	0		0	0	0	0	0	0	0
Molindone (Mobane)	0	0	0	2	0	2	0	0	0	0	0	0		0	0	0	0	0	0
Perphenazine (Trilafon)	0	6	6	3	0	15	0	0	0	1	0	0	1		0	0	0	0	2
Pimozide (Orap)	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	0	0	0
Thioridazine (Mellaril)	0	6	1	8	0	15	1	0	1	0	0	0	0	0	0		0	1	3
Thiothixene (Navane)	0	10	3	5	0	18	1	0	0	0	0	0	0	0	0	1		0	2
Trifluoperazine (Stelazine)	0	12	3	2	1	18	2	0	0	0	0	0	0	0	0	1	0		3
First Generation Antipsychotics	0	63	35	40	4	142	6	0	3	1	0	0	2	1	0	5	1	4	23

Table I-6: Bivariate analysis of demographic, clinical, and employment factors associated with use of a first or second generation antipsychotic in the population diagnosed with schizophrenia

		First Generation Antipsychotic		Second Generation Antipsychotic		p-value
		N	%	N	%	
Age	mean (SD)	47.1	10.8	44	12.4	<0.0001
Gender	Male	404	30.2	932	69.8	0.836
	Female	569	29.9	1,334	70.1	
Location	Rural	186	30.7	419	69.3	0.676
	Non-Rural	787	29.9	1,847	70.1	
	North East	275	32.7	565	67.3	0.048
	Not North East	698	29.1	1,701	70.9	
	North Central	248	27.0	669	73.0	0.019
	Not North Central	725	31.2	1,597	68.8	
	South	401	30.4	920	69.6	0.745
	Not South	572	29.8	1,346	70.2	
	West	46	30.3	106	69.7	0.951
	Not West	927	30.0	2,160	70.0	
Diagnoses	Bipolar Disorder	295	24.3	917	75.7	<0.0001
	No Bipolar Disorder	678	33.5	1,349	66.5	
	Anxiety	103	25.8	297	74.2	0.046
	No Anxiety	870	30.6	1,969	69.4	
	Depression	211	24.2	622	75.8	<0.0001
	No Depression	762	32.2	1,604	67.8	
	Other Mental Health	495	25.2	1,468	74.8	<0.0001
	No Other Mental Health	478	37.5	798	62.5	
	Diabetes	203	34.9	379	65.1	0.005
	No Diabetes	770	29.0	1,887	71.0	
Switching	Switched To	131	18.7	571	81.3	<0.0001
	Not post switch	842	33.2	1,695	66.8	
Combinations	Combined	143	34.0	278	66.0	0.060
	Not Combined	830	29.5	1,988	70.5	
Employment	Full Time	1,013	44.7	1,253	55.3	0.146
	Part Time / Retired / Unemployed	462	47.5	511	52.5	
	Responsible for Coverage	1,200	53.0	1,066	47.0	0.696
	Dependent	508	52.2	465	47.8	
	Salary	1,754	77.4	512	22.6	0.038
	Non-Salary / Unknown	785	80.7	188	19.3	
	Hourly	1,643	72.5	623	27.5	0.090
	Non-Hourly / Unknown	677	69.6	296	30.4	

Table I-7: Bivariate analysis of demographic, clinical, and employment factors associated with switching between and combinations of antipsychotics in the population diagnosed with schizophrenia

		Switching					Combination				
		Switch		Non-Switch		p-value	Combination		Non-Combination		p-value
		N	%	N	%		N	%	N	%	
Age	mean (SD)	43.3	12.3	45.2	12.0	0.000	44.9	11.6	44.8	12.1	0.857
Gender	Male	272	20.4	1,064	79.6	0.128	172	12.9	1,164	87.1	0.861
	Female	430	22.6	1,473	77.4		249	13.1	1,654	86.9	
Location	Rural	128	21.2	477	78.8	0.733	69	11.4	536	88.6	0.196
	Non-Rural	574	21.8	2,060	78.2		352	13.4	2,282	86.6	
	North East	172	20.5	668	79.5	0.328	140	16.7	700	83.3	0.000
	Not North East	530	22.1	1,869	77.9		281	11.7	2,118	88.3	
	North Central	197	21.5	720	78.5	0.869	124	13.5	793	86.5	0.577
	Not North Central	505	21.7	1,817	78.3		297	12.8	2,025	87.2	
	South	285	21.6	1,036	78.4	0.910	132	10.0	1,189	90.0	<0.0001
	Not South	417	21.7	1,501	78.3		289	15.1	1,629	84.9	
	West	43	28.3	109	71.7	0.043	23	15.1	129	84.9	0.423
	Not West	659	21.3	2,428	78.7		398	12.9	2,689	87.1	
Diagnoses	Bipolar Disorder	337	27.8	875	72.2	<0.0001	145	12.0	1,067	88.0	0.176
	No Bipolar Disorder	365	18.0	1,662	82.0		276	13.6	1,751	86.4	
	Anxiety	115	28.8	285	71.3	0.000	34	8.5	366	91.5	0.004
	No Anxiety	587	20.7	2,252	79.3		387	13.6	2,452	86.4	
	Depression	263	30.1	610	69.9	<0.0001	96	11.0	777	89.0	0.040
	No Depression	439	18.6	1,927	81.4		325	13.7	2,041	86.3	
	Other Mental Health	517	26.3	1,446	73.7	<0.0001	248	12.6	1,715	87.4	0.445
	No Other Mental Health	185	14.5	1,091	85.5		173	13.6	1,103	86.4	
	Diabetes	139	23.9	443	76.1	0.153	80	13.7	502	86.3	0.554
	No Diabetes	563	21.2	2,094	78.8		341	12.8	2,316	87.2	
Switching	Switched To	N/A	N/A	N/A	N/A	N/A	3	0.4	699	99.6	<0.0001
	Not post switch	N/A	N/A	N/A	N/A		418	16.5	2,119	83.5	
Combinations	Combined	3	0.7	418	99.3	<0.0001	N/A	N/A	N/A	N/A	N/A
	Not Combined	699	24.8	2,119	75.2		N/A	N/A	N/A	N/A	
Employment	Full Time	394	22.3	1,370	77.7	0.317	198	11.2	1,566	88.8	0.001
	Part Time / Retired / Unemployed	308	20.9	1,167	79.1		223	15.1	1,252	84.9	
	Primary Policy Holder	316	20.6	1,215	79.4	0.177	181	11.8	1,350	88.2	0.060
	Dependent	386	22.6	1,322	77.4		240	14.1	1,468	85.9	
	Salary	152	21.7	548	78.3	0.976	100	14.3	600	85.7	0.252
	Hourly / Unknown	550	21.7	1,989	78.3		321	12.6	2,218	87.4	
	Hourly	189	20.6	730	79.4	0.336	114	12.4	805	87.6	0.528
	Salary / Unknown	513	22.1	1,807	77.9		307	13.2	2,013	86.8	

Table I-8: Model fitting diagnostics for variables associated with the use of first or second generation antipsychotics, adherence, persistence, switching, and combination in the schizophrenia population

Dependent Variable	Iteration	Description	Log Likelihood	-2 Log Likelihood	Model DF	DF from previous model	chi-square critical value	P-value
Second Generation Antipsychotic Use	1	Full Model*	3800.453		14			
	2	Full Model - Salary	3800.474	0.042	13	1	3.84	>0.05
	3	Full Model - Salary, Full	3801.677	2.406	12	1	3.84	>0.05
	4	Full Model - Salary, Full Time, Comb	3801.83	0.306	11	1	3.84	>0.05
	5	Full Model - Salary, Full Time, Comb, Anxiety	3801.83	0	10	1	3.84	>0.05
	6	Full Model - Salary, Full Time, Comb, Anxiety,	3803.586	3.512	9	1	3.84	>0.05
	7	Full Model - Salary, Full Time, Comb, Anxiety, Depression, Region	3811.36	15.548	6	3	7.81	<0.05

*Full model includes: Age, gender, region, diagnoses, switching, combination, and employment variables

**Final model includes: Age, gender, region, diagnosis, and combination

Dependent Variable	Iteration	Description	Log Likelihood	-2 Log Likelihood	Model DF	DF from previous model	chi-square critical value	P-value
Switching	1	Full Model*	3224.655		14			
	2	Full Model - Covered**	3225.013	0.716	13	1	3.84	>0.05
	3	Full Model - Covered, Region	3229.903	9.78	10	3	7.81	<0.05

*Full model includes: Age, gender, region, diagnoses, use of second generation antipsychotic, combination, and responsibility for co

**Final model includes: Age, gender, region, diagnoses, use of second generation antipsychotic, and combination

Dependent Variable	Iteration	Description	Log Likelihood	Difference in -2 Log Likelihood	Model DF	Difference in DF from previous model	chi-square critical value	P-value
Combination	1	Full Model*	2259.84		17			
	2	Full Model - Rural	2259.84	0	16	1	3.84	>0.05
	3	Full Model - Rural, SGA	2260.001	0.322	15	1	3.84	>0.05
	4	Full Model - Rural, SGA, Depression	2260.152	0.302	14	1	3.84	>0.05
	5	Full Model - Rural, SGA, Depression, Other Mental Health	2261.22	2.136	13	1	3.84	>0.05
	6	Full Model - Rural, SGA, Depression, Other Mental Health, Bipolar Disorder	2261.257	0.074	12	1	3.84	>0.05
	7	Full Model - Rural, SGA, Depression, Other Mental Health, Bipolar Disorder, Diabetes**	2262.092	1.67	11	1	3.84	>0.05
	8	Full Model - Rural, SGA, Depression, Other Mental Health, Bipolar Disorder, Diabetes, Region	2285.674	47.164	8	3	7.81	<0.05

*Full model includes: Age, gender, rural / non-rural, region, diagnoses, use of second generation antipsychotic, switching, and emplo

**Final model includes: Age, gender, region, diagnosis of anxiety, switching, and employment variables

Table I-9: Odds Ratios for the likelihood that a patient would receive a second generation antipsychotic as compared with a first generation antispychotic

		Point Estimate	95%Confidence Limits	
Demographic	Male	0.919	0.783	1.08
	Age	0.981	0.974	0.988
Region	North East	Reference		
	North Central	1.3	1.053	1.603
	South	1.188	0.982	1.439
	West	0.919	0.624	1.354
Clinical	Bipolar	1.271	1.072	1.507
	Other Mental Health	1.489	1.266	1.75
	Diabetes	0.852	0.698	1.039
	Switch	1.937	1.568	2.393

Table I-10: Odds Ratios for the likelihood that a patient would switch treatments, according to selected demographic and clinical characteristics.

		Point Estimate	95%Confidence Limits	
Demographic	Male	0.93	0.774	1.116
	Age	0.993	0.986	1.001
Region	North East	Reference		
	North Central	1.053	0.832	1.333
	South	1.145	0.92	1.425
	West	1.539	1.027	2.306
Clinical	Second Generation Antipsychotic	1.929	1.561	2.384
	Anxiety	1.17	0.912	1.501
	Bipolar	1.393	1.163	1.668
	Depression	1.435	1.181	1.744
	Other Mental Health	1.592	1.301	1.949
	Diabetes	1.345	1.081	1.695

Table I-11: Odds Ratios for the likelihood of combination antipsychotic medication treatment, according to selected demographic and clinical characteristics.

		Point Estimate	95%Confidence Limits	
Demographic	Male	0.94	0.748	1.182
	Age	0.995	0.985	1.005
Region	North East	Reference		
	North Central	0.727	0.554	0.955
	South	0.534	0.411	0.694
	West	0.958	0.58	1.582
Clinical	Anxiety	0.643	0.44	0.94
	Switch	0.021	0.007	0.067
Employment	Full Time	0.653	0.523	0.989
	Responsible for Coverage	0.785	0.623	0.815

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CHAPER 2

ADHERENCE TO ANTIPSYCHOTIC TREATMENTS IN A COMMERCIALLY INSURED POPULATION DIAGNOSED WITH SCHIZOPHRENIA

Formatted for submission to the Journal of Managed Care Pharmacy (JMCP), not yet submitted.

Abstract:

Background

Adherence and persistence to medications for schizophrenia is typically less than that seen in other classes of medication. Additionally, studies of adherence to antipsychotics are often completed in populations with a high prevalence of schizophrenia, which may not be generalizable to the commercially insured population. The purpose of this analysis was to determine the factors associated with adherence to therapy in a commercially insured population.

Methods

A retrospective cohort study was completed in order to determine if demographic, clinical, or employment characteristics described in administrative claims data are associated with adherence and persistence in this population. Adherence was calculated based on a medication possession ratio of greater than 80%, and persistence was based on a gap of 90 days or more in therapy.

Results

There were 1,086 individuals identified with an ICD-9 code indicating schizophrenia and at least 2 dispensings of the same medication. The adherence rate observed in this population was 61.3% (N=666), with 70.4% (N=765) experiencing no 90 day gaps in therapy. After adjusting using logistic regression, good adherence was associated with documentation of diabetes (OR 0.691, 95% CI 0.501 - 0.952) or mental health comorbidities (OR 0.587, 95% CI 0.457 - 0.755). Poor persistence on therapy was associated with anxiety (OR

0.691, 95% CI 0.501 - 0.952) or bipolar disorder (OR 0.587, 95% CI 0.457 - 0.755).

Conclusion

Several factors drive an individual's adherence and persistence to medication regimens. Adherence and persistence were both decreased in individuals with comorbid mental health conditions such as bipolar disorder or anxiety. Demographic and employment characteristics were not significant predictors of adherence or persistence.

Background:

Prevalence of Schizophrenia

Treatment of Mental health disorders can be difficult and expensive, and these conditions occur fairly commonly in the United States. The lifetime prevalence of schizophrenia is between 0.3% and 1.6%,[1] with the period prevalence of schizophrenia between 0.13% and 0.82%.[2] Although less common in commercially insured populations, the prevalence of schizophrenia in that group is still not negligible at about 0.13%.[3] Despite being less prevalent in the commercial population overall, people in this group make up a significant portion (16%) of the schizophrenic population.[3]

Antipsychotic Treatment

Adherence to treatment is a key stumbling block for many patients receiving antipsychotics. A review of the literature by Llorca found that several studies demonstrate a significant relationship between low adherence and relapses and hospitalization.[4] The difficult side effects of antipsychotics, which include extrapyramidal effects in first generation antipsychotics and metabolic effects in second generation antipsychotics, alone are a barrier to adherence. A study by Bulloch found that 35% of individuals were non-adherent to their antipsychotics,[5] and Second Generation Antipsychotics were associated with a

better likelihood of adherence than First Generation Antipsychotics in several studies.[6, 7]

Less complicated regimens[8], levels of social support,[9] and patient attitude towards treatment are additional areas associated with patient adherence.[10] It has also been demonstrated that treatment naïve patients are less likely than those who have switched from another medication to be adherent and persistent,[11] demonstrating the difficulty in selecting a first medication.

In the schizophrenia population, it is clear that decreased adherence leads to a decreased treatment response,[12] a higher rate of relapse,[13, 14] and greater risk of hospitalization.[15-17] The Law study in particular found that within 10 days of a missed refill, the risk of hospitalization increases significantly.[17] In schizophrenic patients, adherence was better on second generation antipsychotics,[18] with Rabinovitch finding that 59.4% of second generation users were adherent, compared to 34.5% of first generation users.[9] Studies have been mixed in their assessment of factors leading to better adherence to antipsychotics in the schizophrenic population, with Acosta, et al, finding no relationship between sociodemographic, clinical, or treatment related variables and adherence,[19] while Valenstein et al found that demographic factors such as younger age and non-white race were associated with poorer adherence, as were clinical factors such as using a second generation antipsychotic.[20]

Similar trends emerge among populations of patients having Bipolar disorder. Such patients utilizing second generation antipsychotics were more likely to be both adherent and persistent, and also less likely to switch.[21] Several

studies of patients having bipolar disorder demonstrate a decrease in hospitalization risk in adherent groups.[22, 23] Bipolar individuals with a medication possession ratio (MPR) greater than 80% decreased their risk of hospitalization by 18%, compared to those considered non-adherent.[23] Barriers such as lacking social support also affect adherence in this population.[24]

Study Purpose and Justification

There have been many studies conducted to better understand factors influencing adherence to antipsychotics. The vast majority of the literature identified above focuses on specific populations with a high incidence of schizophrenia, those individuals utilizing Medicaid and Veteran's Administration (VA) programs. The commercial population likely differs significantly from the Medicaid and VA groups where patients are typically older, and (especially in the VA) more likely to be male.[7, 25] This population is also different from those used in prospective open-label trials such as CATIE, in which 85% of the population was unemployed.[26] It is critical to gain a better understanding of medication utilization patterns the commercial population. Sixteen percent of schizophrenic patients receive services through private insurance, and represent a fairly significant cost in this population.[3] Programs designed to better manage these populations will utilize the improved information to better understand their participants, leading to more targeted interventions.[27, 28]

In addition to better understanding this population, there are also a wide variety of methods utilized to measure adherence to antipsychotics described in the literature, although the MPR method is most common.[17, 29, 30] MPR and proportion of days covered (PDC) have both been shown to be associated with poor outcomes such as hospitalization.[29] Additionally, evaluating large gaps in therapy as a proxy for discontinuation provides insight into longer drug free periods and may be associated with different factors than MPR and PDC.[17]

The goal of this analysis was to evaluate factors that may be associated with medication adherence among commercially insured patients utilizing antipsychotic medications, considering both MPR results and drug discontinuation. These factors include: the use of first or second generation agents, switching treatments, use of combination treatments, and the demographic, clinical, and employment characteristics of the population.

Methods:

Study Design:

Data from the Thompson MarketScan database were utilized to conduct a retrospective cohort analysis of medication adherence in the schizophrenic population utilizing antipsychotics. The outcome of interest in this analysis is the Medication Possession Ratio (MPR), indicating how closely a patient complies with the medication regimen during treatment periods. The association between clinical, demographic, and employment factors on MPR are evaluated based on multivariate statistical analysis.

Data Source:

The data source for this analysis is the Thomson MarketScan commercial claims dataset, including employees and their dependents working for large companies spread across the United States, and insured by roughly 100 different payers. This data set contains comprehensive medical, demographic, and employment data for roughly 5.9 million individuals between 2000 and 2001. The data is provided in cleaned data sets, but it was still examined in order to ensure that variables were complete and distributed as expected.

Inclusion Criteria:

From the overall eligible population (N = 1,428,349), 2,156 individuals (0.15%) were identified as schizophrenic, and 1,361 of those had at least one treatment episode where MPR could be calculated. Inclusion criteria for this analysis require that a patient be continuously enrolled for the entire study period (24 months), and be between 18 and 65 years of age at the beginning and end of the study. The individuals must also have at least 1 ICD-9 code indicating schizophrenia (295.xx), and 2 dispensings for the same antipsychotic medication occurring within the period. Figure II-1 demonstrates the sample selection criteria.

Operational Definitions:

Continuous enrollment was defined as having 366 days of continuous enrollment in 2000, and 365 days of continuous enrollment in 2001 with both medical and pharmacy coverage. This data was abstracted from the enrollment data sets provided.

Diagnoses for specific conditions were identified through the presence of one or more ICD-9 codes in the inpatient or outpatient records. Anxiety, Bipolar Disorder, Depression, Schizophrenia, and Other Mental Health Disorders not included above (such as substance abuse) were identified. Documentation of Diabetes was also identified due to the association between second generation

antipsychotics and an increased risk of metabolic outcomes. The specific list of ICD-9 codes used to identify these conditions is provided in table II-1. This methodology is similar to that used in a variety of other studies,[3, 18, 21, 32] and validated by Rawson, et al, in 1997.[32]

Therapy with a given treatment was defined as receipt of at least 2 dispensings of that medication within the study period. The "therapeutic period" for a treatment is the time from the first fill, to the date of the last fill plus the last days supply, and any days spent in the hospital. "Combination Therapy" is defined as two treatments overlapping by a minimum of 90 days. A "switch" in therapy was defined as a change from one treatment to another where there is no more than a 90 day gap in therapy, and no more than 90 days of overlap in therapy. A discontinuation in treatment is defined as a period of 90 days or more without therapy following the end of a therapeutic period, excluding any days in the hospital. Studies have typically used periods of 30 to 90 days to define gaps in therapy.[18, 21, 33] This study utilized the 90 day period to match the longest days supply routinely received by patients.

Adherence was calculated utilizing the Medication Possession Ratio (MPR), calculated utilizing equation 1 below.[20] Although a variety of methodologies for measuring adherence are available, several methods such as electronic monitoring (MEMS caps), or patient questionnaires are not feasible. Although electronic monitoring is considered the gold standard,[19] use of medical records or claims databases are considered more accurate than patient self-report.[19, 34, 35] The decision to use MPR rather than Proportion of Days Covered

(PDC) was based on several studies supporting its use,[6, 36, 37] as well as it being the most common measure reported in the literature, and therefore the best for comparison amongst studies. Any days spent in the hospital were removed from the time period between the first and last fills.

Equation 1:

$$MPR = \frac{\left(\sum day\_qty\right) - last\_day\_qty}{Last\_fill\_date - First\_fill\_date}$$

Therapy duration was calculated as the difference between the end of the treatment period and the first fill date, similar to several studies reported in the literature.[18, 21, 38] One treatment period was identified for each individual based on whichever medication, or combination of medications, they were using as of January 1, 2001. Discontinuation was defined as having a therapy end date prior to September 30, 2001, and no other antipsychotic treatments between that date and the end of the study period.

Demographic variables were cleaned and defined as well. An individual's age was defined as the difference between their birth year, and the year 2000. There were no instances in the data where an individual had more than 1 gender on record. Employment and geographic variables were defined for each individual as the value that turned up most often for that individual (if more than one value was available). Employment characteristics included full time vs. part time or unemployed status, primary vs. dependent coverage status, and salary vs. hourly pay. Geographic variables were coded as rural or non-rural based on

Metropolitan Statistical Area, and Region (North East, North Central, South, and West).

Bivariate analysis

Because of the typical left skewed, truncated nature of the distribution of MPR, each individual treatment episode was categorized as adherent (MPR ≥80%) or non-adherent (MPR <80%). The 80% cut-off has been utilized as the threshold in several publications describing adherence rates and outcomes due to poor adherence in populations treated for psychiatric conditions including schizophrenia.[18, 21, 38] Treatment gap of 90 days or more was treated as a dichotomous variable. The relationship between the outcomes of interest (adherence and discontinuation) and the clinical and demographic variables (first or second generation antipsychotic utilization, treatment combination or switch, demographic, and employment variables) was tested using the chi-square analysis. The association between age, the only continuous explanatory variable, and adherence and discontinuation was also tested utilizing the student's T-test.

Multivariate Analysis:

Two separate Logistic regression models were used in order to adjust for multiple factors influencing MPR and discontinuation. Adherence to therapy was modeled against first or second generation medication choice, switching, combination use, demographic, clinical, and employment factors. Interaction

terms including the various combinations of age group, gender, and comorbidities were also included if they were associated with the dependent variable as measured by the chi-square test with a significant p-value (<0.2). Chi-square analysis was also used to assess several potential associations amongst independent variables to determine if they were independent. If the variables were not independent (chi-square value was less than 0.05), the less important variable was dropped from consideration for the model. Stepwise backwards elimination was used to optimize the model, using the -2 log likelihood to test the significance of changes. Multicollinearity was assessed based on the variation inflation factor (VIF), and eignevalues. These were calculated utilizing a separate model with the proc reg function in SAS with the VIF, TOL, and collin options. If the condition number was greater than 30, or the VIF was greater than 5, increased scrutiny was given to the affected variables. Hosmer-Lemeshow was used to assess goodness of fit.

Results:

Univariate results:

In the first year of data, 2,156 (0.2% of those meeting demographic criteria) individuals were identified with at least 1 ICD-9 code indicating schizophrenia, of them 1,086 (50.3%) individuals that had at least 2 dispensings of the same medication within 90 days of each other to create a treatment episode including January 1, 2001. The demographic, clinical, and employment characteristics of the population are described in table II-2. Of the 1,086 individuals that had treatments, 666 (61.3%) were considered adherent. Most of the treatment episodes in this analysis were for second generation antipsychotics, with 15.1% following a switch in therapies, and 13.8% received in combination. Table II-3 provides a description of the therapies observed in this population.

The mean duration of treatment without any gaps over 90 days between January 1, 2000 and December 31, 2001 was 579.2 (sd 173.1) days. Duration had a bimodal distribution due to the short time period of the data, with peaks at 450 and 750 days (figure II-2). 698 (64.2%) episodes were likely began therapy prior to the earliest records in the data, 765 (70.4%) likely continued therapy beyond the study period, and 541 (49.8%) were began prior to and ended after the study period. The minority, 164 (15.1%) of episodes occur completely within the study period.

Bivariate results:

The bivariate analyses demonstrated that older age was associated with greater adherence: (46.9 [sd 11.3] in the adherent group vs. 45.2 [sd 11.9] in the non-adherent group, p=0.014). Age groupings did not show any statistically significant difference in adherence. Gender was not associated with adherence. Patients also having diabetes were significantly less likely to be adherent to therapy than non-diabetics (55.0% vs. 62.8% respectively, p=0.042). Hourly workers were more likely than others to be adherent (67.1% vs 59.5% salaried and 58.9% others, p=0.0487). The remaining results are listed in table II-4.

Discontinuation was identified in 321 (29.6%) individuals. These individuals tended to be younger, with 18 to 44 year olds discontinuing 33.4% vs 27.3% in 45 to 64 year olds (p = 0.033). Individuals with additional mental health diagnoses were also significantly more likely to discontinue therapy (36.0% vs 23.1% [p<0.001] for those with no comorbid mental health conditions documented). Individuals who combined medications (47.3% vs. 26.7% [p<0.001] for those that did not combine) or switched between medications (37.8% vs. 28.1% [p=0.012] for those that did not switch) were also more likely to discontinue therapy. Table II-5 provides the percent of individuals who discontinued and the p-values for all of the variables examined.

Multivariate results:

The multivariate analysis found several associations between adherence and clinical, demographic, and employment related factors. Table II-6 provides the diagnostic data utilized in fitting the final model. Adherence was modeled against age, gender, comorbid diagnoses, use of a second generation antipsychotic, switching, combination use, and payer type. All variables remained in the final model. This model had a good fit, with c=0.842, and Hosmer-Lemeshow p-value = 0.401. Individuals with a comorbid diagnosis of diabetes (OR 0.691, 95% CI 0.501 – 0.952) or other mental health conditions such as substance abuse (OR 0.587, 95% CI 0.457 – 0.755) were both less likely to be adherent to their antipsychotic treatments. Other variables did not result in significant differences in MPR. Table II-7 provides the odds ratios associated with the remaining variables.

There were fewer significant associations between discontinuation and the demographic, clinical, and employment characteristics tested. The full model included age, gender, diagnosis of anxiety, bipolar disorder, depression, other mental health diagnoses, first or second generation antipsychotic use, switching, combination use, and insurance coverage type (primary vs. dependent). The final model included age, gender, comorbid diagnoses, and use of combinations (table II-8). Goodness-of-fit for this model was adequate with c-statistic = 0.747, and Hosmer-Lemeshow p-value = 0.495. Documentation of bipolar disorder (OR 0.587, 95% CI 0.457 - 0.755) and anxiety (OR 0.691, 95% CI 0.501 - 0.952) were

both associated with less likelihood to be persistent. Table II-9 provides the odds ratios from the final model.

Discussion:

This analysis demonstrates the importance of comorbidities in the likelihood that a patient will be adherent to and persistent on therapy. Observed decreases in adherence associated with a diabetes or other mental health diagnoses may lead to treatment being ineffective, with resultant increases in the need for medical care, as well as increases in the indirect costs of schizophrenia. This analysis gives caregivers, providers, and insurers new insight into the factors that increase the risk of non-adherence and non-persistence in the commercial population, and these can be utilized to identify the patients who would be the best targets for outreach attempting to improve adherence.

Factors Associated with MPR

Adherence measured by MPR is the most commonly utilized methodology in literature addressing claims based studies. The adherence rate found in our study (61.3% of the population having an MPR above 80%) is higher than that seen in other studies, for example Ascher-Svanum found that 58% of participants in the US Schizophrenia Care and Assessment Program (US-SCAP) had an MPR above 80%, Valenstein found that 60% of the VA population studied had an MPR greater than 80%, and Gilmer found that only 41% of the Medicaid population they studied was adherent using the same criteria.[20, 38, 39] There are a number of potential explanations for this finding. First, studies have shown that

social support is a key driver of adherence,[9] in this analysis dependents tended to be more adherent than primary policy holders, thus dependent status may be an indicator of the social support available to these individuals. In addition to differences in the population, there may also be differences in the methodology used to calculate MPR, where some studies do not exclude days in the hospital from the denominator, or use the entire study period as the denominator, rather than just the treatment period.

The multivariate results show that certain clinical characteristics are key drivers associated with adherence. There are differing reports on superior adherence rates in first vs. second generation antipsychotic users, with a VA population having lower adherence to second generation antipsychotics (62.2% and 58.8% with an MPR >80% in first vs. second generation antipsychotics respectively),[20] and a study based on patients with a first episode of psychosis in the community found that second generation antipsychotics resulted in better adherence (MPR = 59.4% vs. 34.5% in first generation users);[6, 9, 20] in the study described here, we found that there was no significant difference in adherence for second generation antipsychotic users as compared to first generation antipsychotic users.

Individuals with other mental health disorders also had lower adherence rates, which correlate with the existing literature.[40] A study by Lang et al found that combination users were more likely to be adherent than those using single treatments (71% in combination users vs. 70% in first generation users and 64% in second generation users), agreeing with our study that found that combination

users trended towards higher adherence than single medication users (OR 1.361, 95% CI 0.939 - 1.972).[40] There was also lower adherence among patients having diabetes in our study, which may be indicative of concern about metabolic adverse events, or associated with increased complexity of care in general.[41] Other studies have also found limited associations between demographic, economic / work, and clinical variables and adherence.[19]

Factors Associated with Persistence

Persistence indicates the length of time an individual is able to remain on treatment. Due to the relatively short timeframe available for this study, most individuals were already on a treatment at the beginning of the study, and still taking it at the end. Therefore we were unable to calculate a true estimation of treatment duration in this population, but with nearly 50% of the population receiving therapy without more than a 90 day gap at the beginning and end of the study, the commercially insured population performs significantly better than the CATIE population, where 74% of new users discontinued therapy by 18 months,[26] as well as a VA population where the median time to discontinuation was 120 days.[33] Being persistent on therapy is crucial as the risk for poor outcomes such as hospitalization can begin to increase in as little as 10 days after discontinuing therapy.[17]

Our study demonstrated an increased risk for discontinuation in populations with comorbid bipolar disorder or anxiety. These conditions likely

complicate therapeutic regimens due to their episodic nature, leading to discontinuations due to changes in overall disease states, but also due to confusion on the part of the individual.[8] Overall, there were very few variables associated with discontinuation following adjustment with logistic regression. This is in agreement with the literature where Gianfrancesco et al found that there was no difference in persistence between first and second generation antipsychotics in a commercial population.[18] In an evaluation of the VA population, there was less likelihood of discontinuation in second generation antipsychotic users as compared to first generation antipsychotic users. Several issues may be causing this difference in outcomes. First, the VA study did not control for comorbid conditions in their analysis. Additionally there are some substantial differences in the populations, with the VA consisting largely of older male patients at the time, and the Medicaid population likely having significant differences in sociodemographic characteristics such as income and social support that could not be measured in either study.

Limitations

Studies utilizing claims records to measure adherence are prone to several well documented limitations. For instance, without observing an individual taking a medication one cannot be sure that it is being taken. Pharmacy claims can also be incomplete if patients receive samples from their

physician, or pay cash rather than their copay for inexpensive generics, resulting in underestimates of adherence.

The short time period available in our data also limited the ability to follow patients over a long period of time based on trade-offs with population size. Future studies using a broader population, and longer timeframe may also be able to identify more significant drivers of adherence and persistence than those seen in our population. The age of this data may also limit generalizability due to the addition of new treatments and changes in guidelines over time. Generalizability is also limited to the commercially insured population represented by the data.

The limitations of claims data might also help to explain why full time workers are less likely to be adherent to therapy. Although our methodology for identifying schizophrenia in the population is in line with several other published studies,[3, 18, 32] requiring only one ICD-9 code for schizophrenia may be allowing some false positives. Although uncommon (Rawson et al found 97% agreement between computerized records and medical charts),[32] if those false positives are represented disproportionately in full time workers, it might be the case that those individuals are more likely to be using these antipsychotics for off-label purposes,[42] such as the use of low dose quetiapine for sleep, which in turn could be lowering their overall possession ratios. Further research to validate the coding of schizophrenia in commercial databases would be necessary to confirm or reject this hypothesis.

Conclusions

Several factors drive an individual's adherence and persistence to medication regimens. Adherence and persistence were both decreased in individuals with comorbid bipolar disorder or anxiety. Demographic and employment characteristics were not significant predictors of adherence or persistence.

Figures:

Figure II-1: Inclusion and exclusion criteria flowchart

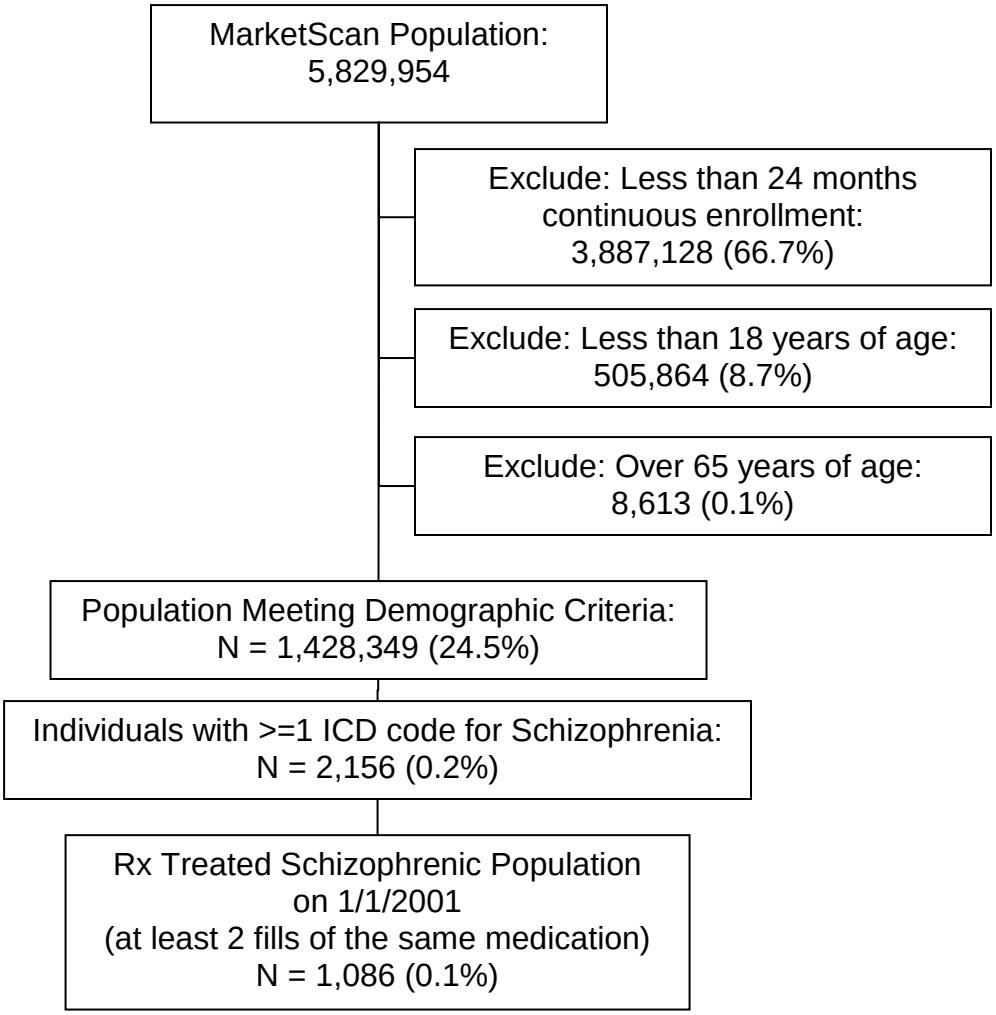
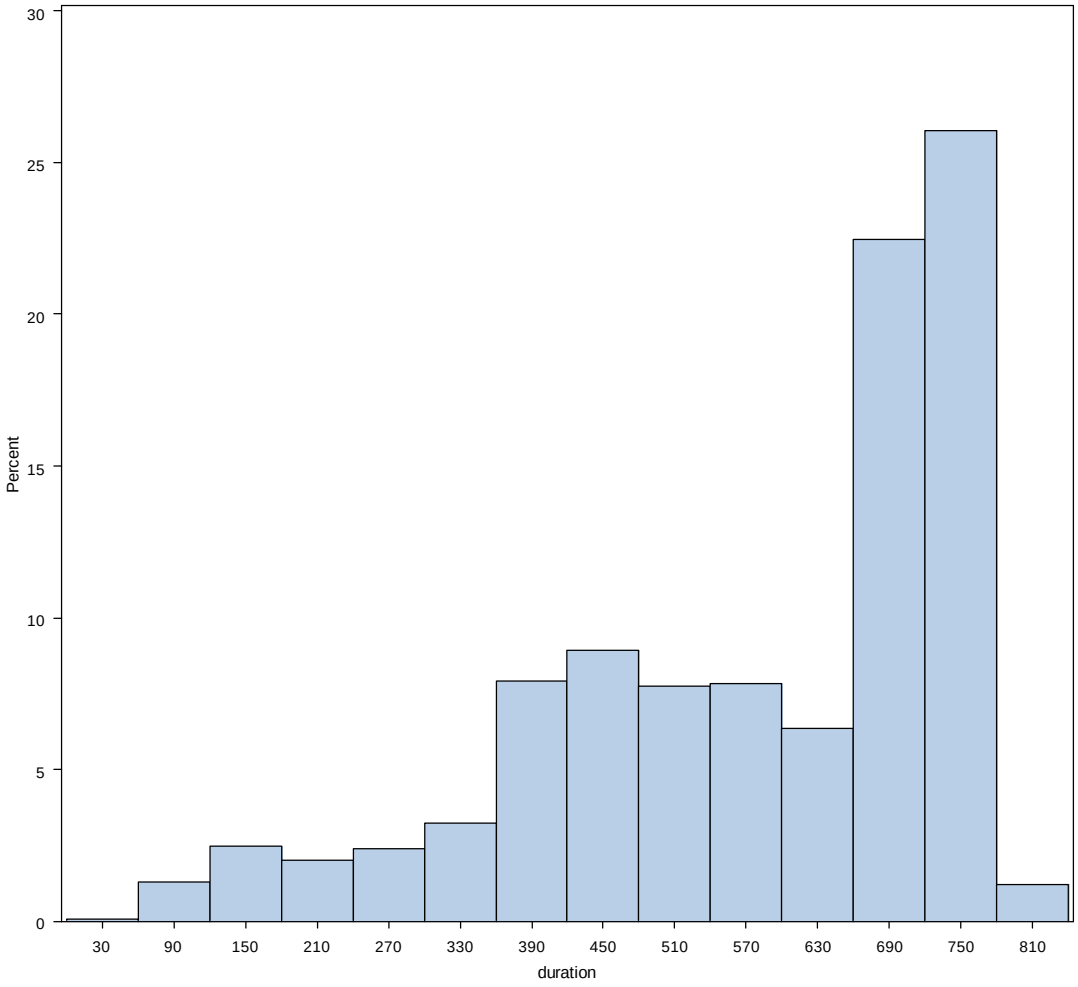


Figure II-2: Histogram of frequency of days of continual antipsychotic treatment among patients with a diagnosis of schizophrenia



Tables:

Table II-1: ICD-9 Codes used for identifying diagnoses with primary conditions and comorbidities

Condition	ICD-9 Codes Included
Schizophrenia	295 - 295.95
Bipolar Disorder	296 - 296.99
Anxiety	300 - 300.09
Depression	311, 300.4
Other Mental Health	290 - 319, except for those listed above
Diabetes	250.00 – 250.99

Table II-2: Demographic characteristics of the study population

		Total (N = 1086)	
		N	% of Total
Age	18 - 44	401	36.9
	45 - 64	685	63.1
Gender	Male	441	40.6
	Female	645	59.4
Location	Rural	203	18.7
	Non-Rural	883	81.3
	North East	306	28.2
	North Central	306	28.2
	South	427	39.3
	West	47	4.3
Diagnoses	Bipolar Disorder	333	30.7
	No Bipolar Disorder	753	69.3
	Anxiety	107	9.9
	No Anxiety	979	90.1
	Depression	239	22.0
	No Depression	847	78.0
	Other Mental Health	545	50.2
	No Other Mental Health	541	49.8
	Diabetes	200	18.4
	No Diabetes	886	81.6
Medication Utilization	Second Generation Antipsychotic	710	65.4
	First Generation Antipsychotic	282	26.0
	Both (combination)	94	8.7
	Switched To	164	15.1
	Not post switch	913	84.1
	Combined	150	13.8
	Not Combined	936	86.2
Employment	Full Time	569	52.4
	Part Time / Retired / Unemployed	517	47.6
	Primary Policy Holder	527	48.5
	Dependent	559	51.5
	Salary	227	20.9
	Hourly	307	28.3
	No Pay / Unknown	552	50.8

Table II-3: Treatments observed in the study population

		N	%
Total Population		1086	100.0%
Second Generation Antipsychotics	Any SGA monotherapy	665	61.2%
	Clozapine (Clozaril)	60	5.5%
	Risperidone (Risperdal)	251	23.1%
	Quetiapine (Seroquel)	85	7.8%
	Olanzapine (Zyprexa)	269	24.8%
First Generation Antipsychotics	Any FGA monotherapy	271	25.0%
	Haloperidol (Haldol)	49	4.5%
	Loxipine (Loxitane)	13	1.2%
	Thioridazine (Mellaril)	31	2.9%
	Molindone (Mobane)	3	0.3%
	Thiothixene (Navane)	39	3.6%
	Pimozide (Orap)	2	0.2%
	Fluphenazine (Prolixin)	30	2.8%
	Mesoridazine (Serentil)	3	0.3%
	Trifluoperazine (Stelazine)	46	4.2%
	Chlorpromazine (Thorazine)	19	1.7%
	Perphenazine (Trilafon)	36	3.3%
Combinations	Any Combination	150	13.8%
	2 or more Second Generations	45	4.1%
	2 or more First Generations	11	1.0%
	First and Second Generation	94	8.7%

Table II-4: Bivariate associations between adherence and demographic, clinical, and employment characteristics

		Adherent (N=666)		Non-Adherent (N = 420)		p-value
		N	% Adherent	N	% Non-Adherent	
Age	18 - 44	238	59.4	163	40.6	0.3067
	45 - 64	428	62.5	257	37.5	
Gender	Male	266	60.3	175	39.7	0.573
	Female	400	62.0	245	38.0	
Location	Rural	120	59.1	83	40.9	0.473
	Non-Rural	546	61.8	337	38.2	
	North East	195	63.7	111	36.3	0.726
	North Central	183	59.8	123	40.2	
	South	258	60.4	169	39.6	
	West	30	63.8	17	36.2	
Diagnoses	Bipolar Disorder	200	60.1	133	39.9	0.569
	No Bipolar Disorder	466	61.9	287	38.1	
	Anxiety	60	56.1	47	43.9	0.240
	No Anxiety	606	61.9	373	38.1	
	Depression	140	58.6	99	41.4	0.323
	No Depression	526	62.1	321	37.9	
	Other Mental Health	298	54.7	247	45.3	<0.001
	No Other Mental Health	368	68.0	173	32.0	
	Diabetes	110	55.0	90	45.0	0.042
	No Diabetes	330	37.2	556	62.8	
Medication Utilization	Second Generation Antipsychotic	433	61.0	277	39.0	0.2435
	First Generation Antipsychotic	168	59.6	114	40.4	
	Both (combination)	65	69.1	29	30.9	
	Switched To	90	54.9	74	45.1	0.066
	Not post switch	567	62.1	346	37.9	
	Combined	101	67.3	49	32.7	0.104
	Not Combined	565	60.4	371	39.6	
Employment	Full Time	339	59.6	230	40.4	0.215
	Part Time / Retired / Unemployed	327	63.2	190	36.8	
	Primary Policy Holder	316	60.0	211	40.0	0.370
	Dependent	350	62.6	209	37.4	
	Salary	135	59.5	92	40.5	0.049
	Hourly	206	67.1	101	32.9	
	No Pay / Unknown	325	58.9	227	41.1	

Table II-5: Bivariate associations between discontinuation and demographic, clinical, and employment characteristics

		No Discontinuation (N = 765)		Discontinued (N = 321)		p-value
		N	%	N	%	
Age	18 - 44	267	66.6	134	33.4	0.033
	45 - 64	498	72.7	187	27.3	
Gender	Male	313	71.0	128	29.0	
	Female	452	70.1	193	29.9	0.7502
Location	Rural	140	69.0	63	31.0	0.609
	Non-Rural	625	70.8	258	29.2	
	North East	213	69.6	93	30.4	0.329
	North Central	225	73.5	81	26.5	
	South	291	68.1	136	31.9	
	West	36	76.6	11	23.4	
Diagnoses	Bipolar Disorder	211	63.4	122	36.6	0.001
	No Bipolar Disorder	554	73.6	199	26.4	
	Anxiety	58	54.2	49	45.8	0.000
	No Anxiety	707	72.2	272	27.8	
	Depression	145	60.7	94	39.3	0.000
	No Depression	620	73.2	227	26.8	
	Other Mental Health	349	64.0	196	36.0	<0.0001
	No Other Mental Health	416	76.9	125	23.1	
	Diabetes	146	73.0	54	27.0	0.380
	No Diabetes	619	69.9	267	30.1	
Medication Utilization	Second Generation Antipsychotic	505	71.1	205	28.9	0.000
	First Generation Antipsychotic	211	74.8	71	25.2	
	Both (combination)	49	52.1	45	47.9	
	Switched To	102	62.2	62	37.8	0.012
	Not post switch	663	71.9	259	28.1	
	Combined	79	52.7	71	47.3	<0.0001
	Not Combined	686	73.3	250	26.7	
Employment	Full Time	408	71.7	161	28.3	0.339
	Part Time / Retired / Unemployed	358	69.1	160	30.9	
	Primary Policy Holder	381	72.3	146	27.7	0.194
	Dependent	384	68.7	175	31.3	
	Salary	163	71.8	64	28.2	0.472
	Hourly	208	67.8	99	32.2	
	No Pay / Unknown	394	71.4	158	28.6	

Table II-6: Logistic regression model optimization for factors associated with adherence

Iteration	Description	Log Likelihood	Difference in -2 Log Likelihood	Model DF	x^2 critical value	P-value
1	Full Model* **	1416.211		9		
2	Full Model - Pay Type	1418.950	5.478	8	3.84	<0.05

*Full model Includes: Age, gender, diagnoses, use of a second generation antipsychotic, switching, combination, insurance coverage, and full time employment

**Final model includes all variables from the full model

Table II-7: Odds ratios for the likelihood that an individual will be adherent to treatment

		Point Estimate	95%Confidence Limits	
Demographic	Male vs. female	0.919	0.712	1.187
	Age 45-64 vs. 18-44	1.11	0.849	1.451
Clinical	Other Mental Health vs. none	0.587	0.457	0.755
	Diabetes vs. no diabetes	0.691	0.501	0.952
	Switch vs. no switch	0.806	0.572	1.137
	Combination vs. no combination	1.361	0.939	1.972
Employment	Salary vs. Hourly Wages	0.903	0.664	1.228

Table II-8: Logistic regression model optimization for factors associated with discontinuation

Iteration	Description	Log Likelihood	Difference in -2 Log Likelihood	Model DF	x^2 critical value	P-value
1	Full Model*	1244.158		11		
2	Full Model - Antipsych Type	1244.56	0.804	9	3.84	>0.05
3	Full Model - Antipsych Type,Insurance	1245.14	1.16	8	3.84	>0.05
4	Full Model - Antipsych Type, Insurance, Switch**	1246.541	2.802	7	3.84	>0.05
5	Full Model - Antipsychotic Type, Insurance, Switch, Anxiety	1249.458	5.834	6	3.84	<0.05

* Full model Includes: Age, gender, diagnoses, use of a second generation antipsychotic, switching, combination, and insurance coverage type

**The final model includes all variables from the full model except use of a second generation antipsychotic, insurance coverage type, and switching

Table II-9: Odds ratios for the likelihood that an individual will be persistent on treatment

		Point Estimate	95%Confidence Limits	
Demographic	Male vs. female	1.042	0.787	1.381
	Age 45-64 vs 18-44	1.222	0.922	1.619
Clinical	Bipolar vs. no bipolar	0.587	0.457	0.755
	Anxiety vs. no anxiety	0.691	0.501	0.952
	Depression vs. no depression	0.806	0.572	1.137
	other mental health diagnosis vs. none	1.361	0.939	1.972
	Combination vs. monotherapy	0.903	0.664	1.228

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CHAPTER 3

ASSOCIATION BETWEEN ADHERENCE AND HOSPITALIZATION IN A COMMERCIALLY INSURED POPULATION RECEIVING ANTIPSYCHOTICS

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Abstract

Background

Adherence to treatments for schizophrenia are associated with significant adverse events that often lead to poor adherence and discontinuation of therapy. The lack of adherence to therapy may limit its effectiveness and be associated with poor outcomes. The purpose of this analysis is to determine if there is a significant difference in mental health associated hospitalization rates for those individuals with high adherence as compared to those with lower rates of adherence.

Methods

This study utilized a matched retrospective cohort design. Data were obtained from the MarketScan database between 2000 and 2001, and included 1,361 schizophrenia patients treated with antipsychotics. Propensity score matching was utilized to control for differences in sociodemographic and clinical factors between the adherent and non-adherent populations. Adherence was defined based on the Medication Possession Ratio (MPR) being greater than or equal to 80%.

Results

Matching was successful in selecting a non-adherent comparison group for 76.5% of the adherent population, with significant support across the full range of propensity scores. The matching process was successful in limiting the differences in demographic and clinical characteristics between the groups. The risk of hospitalization was higher in the non-adherent population (RR 1.55, 95%

CI 1.07 – 2.25) than the adherent population after matching. This is slightly lower than the relative risk seen in the unmatched group (RR 1.74, 95% CI 1.22 – 2.49 in the adherent population vs. the non-adherent population).

Conclusion

Adherence to antipsychotic treatment has a significant association with a lower likelihood of hospitalization in the schizophrenia population. Additional analysis is necessary to understand the impact of persistence, and other medication taking behaviors such as switching or polytherapy.

Background

Schizophrenia

Mental health disorders are prevalent in the United States, and treating these conditions can be difficult and expensive. A study conducted by Kessler, et al, found that the lifetime prevalence of schizophrenia is between 0.3% and 1.6%.[1] A systematic review of the literature found that the period prevalence of schizophrenia is between 0.13% and 0.82%.[2] An evaluation of a commercially insured population found that the prevalence of schizophrenia in that group is near the lower end of the range, at about 0.13%.[3] Despite being less prevalent in the commercial population, people in this group make up a significant portion (16%) of the schizophrenic population.[3]

Treatments and Adherence

Adherence to treatment is a key stumbling block for many patients receiving antipsychotics. It can take up to 16 weeks for a treatment regimen to become effective for relieving symptoms, but adverse events can occur far earlier.[4] A review of the literature by Llorca found that several studies demonstrate a significant relationship between low adherence and poor outcomes. [5] The side effects of antipsychotics alone are a barrier to adherence. These adverse events are largely metabolic for second generation antipsychotics, while first generation antipsychotics are associated with

extrapyramidal side effects. A study by Bulloch found that 35% of individuals were non-adherent to their antipsychotics, [6] and second generation antipsychotics were associated with a better likelihood of adherence than first generation antipsychotics in several studies.[7, 8]

Less complicated regimens, [9] levels of social support, [10] and patient attitude towards treatment are additional areas associated with improved patient adherence. [11] It has also been demonstrated that treatment naïve patients are less likely than those who have switched from another medication to be adherent and persistent, [12] demonstrating the difficulty in selecting a first medication.

Adherence rates in the literature vary substantially depending on the population, and methods used to measure it. The medication possession ratio (MPR) is based on the sum of the days supply divided by the duration of therapy, whereas the proportion of days covered (PDC) is the number of days with therapy available divided by the length of the study.[13] Individuals with a diagnosis of schizophrenia and a medication possession ratio (MPR) greater than 80% range between 35% and 60%,[6, 14-17] coincidentally, the average MPR or PDC also ranged between 35% and 60% in different studies.[8, 10] This demonstrates the importance of ensuring that results are interpreted with population differences in mind, as results from one group may not be generalizable to another.

Impact of Poor Adherence

Non-adherence to medications leads increasingly poor outcomes over time.[5] Poor adherence is a key driver of relapses in schizophrenia, leading to costs that are 3 times higher than non-relapsers.[18] One key driver of this cost is hospitalization. A Canadian study in 2006 found that individuals who had a medication possession ratio (MPR) of greater than 80% had 63% fewer hospitalizations.[19] A Medicaid population in Wisconsin had twice as many hospitalizations in the non-adherent group, and costs were 4 times higher.[20] The risk of hospitalization increases quickly following discontinuation, with a study by Law et.al. observing the risk increase in as little as 10 days.[21]

Medication therapy choice regarding switching, combination therapy, and use of first vs. second generation antipsychotics might also impact hospitalization rates. In a Medicare population, second generation antipsychotic users and those on combination therapy were more likely to be hospitalized as compared with those utilizing first generation antipsychotics without combining, although the impact of adherence was not addressed in this analysis.[22]

Study Purpose and Justification

It has been estimated that hospitalizations could be decreased by 12.3% in the Medicaid population, saving $103 million per year in the United States if gaps in therapy of longer than 15 days could be eliminated.[23] Interventions have

been successful in improving adherence rates, but additional information regarding the causes of adherence, and the populations where non-adherence is most likely could make these programs more effective.[24] A key to making this information useful is ensuring that it is generalizable to the population where these programs are implemented.

There have been many studies conducted to better understand the factors leading to hospitalizations in the schizophrenia population. The vast majority of the literature identified above focuses on specific populations with a high incidence of schizophrenia, those individuals utilizing Medicaid and VA programs. The commercial population likely differs significantly from the Medicaid and VA groups where patients are typically older, and (especially in the VA) more likely to be male.[22, 23, 25] This population is also different from that identified in Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), a prospective comparative effectiveness trial, in which 85% of the population was unemployed.[26] A better understanding of medication use within the commercial population is critical. Sixteen percent of schizophrenics receive services through private insurance, and represent a fairly significant cost in this population. [3]

The purpose of this study is to determine the association between adherence to antipsychotics and decreased rates of hospitalization, while controlling for other medication taking behaviors and patient characteristics that could be associated with increased hospitalization rates in the commercially insured population receiving antipsychotics.

Methods

Study Design

A matched retrospective cohort study was conducted. Individuals who were adherent to antipsychotics were matched to non-adherent individuals based on propensity scores measuring the likelihood of adherence to medication. Medication taking characteristics were examined for 1 year prior to the admission date of the hospitalized patient and in their non-hospitalized match.

Data

Data for this analysis was made available through the Thomson Medstat dissertation support program. This program provides access to de-identified data in the MarketScan database from years 2000 and 2001. This database contains enrollment and demographics data, as well as medical and pharmacy claims for nearly 5.9 million individuals.

Inclusion Criteria

Individuals were considered for inclusion in this study if they have at least 1 ICD-9 code indicating schizophrenia, 24 months of continuous enrollment, at least 2 fills of an antipsychotic medication in year 1, and are between 18 and 64

years old in the year 2000. Individuals were excluded if they were hospitalized for a mental health condition any time during the first year of the study. Figure III-1 describes the inclusion waterfall.

Operational Definitions

Operational definitions have largely been carried over from the work done previously to describe the antipsychotic using population. Continuous enrollment was defined as having 366 days of continuous enrollment in 2000, and 365 days of continuous enrollment in 2001 with both medical and pharmacy coverage. This data was abstracted from the enrollment data sets provided.

Hospitalizations were based on those individuals hospitalized for a mental health condition as defined by any inpatient record with a Major Diagnostic Category of 19, indicating treatment was for “Mental Diseases and Disorders.” The hospitalization date was based on the related first hospital admission in 2001. Non-hospitalized patients were any individuals that did not have any hospitalizations for a mental health condition as defined above during the study period.

Diagnoses for specific conditions were identified through the presence of ICD-9 codes in the inpatient or outpatient records. Anxiety, Bipolar Disorder, Depression, Schizophrenia, Other Mental Health Disorders not included above, and Diabetes were all identified. The specific list of ICD-9 codes used to identify these conditions is provided in table III-1. The use of documentation of ICD-9

codes to identify schizophrenia and comorbidities matches the methodology used in a variety of other studies, [3, 27, 28] and is similar to methodology utilizing hospitalization billing records validated by Rawson, et al, in 1997. [29]

Therapy with a given treatment was defined as receipt of at least 2 fills within the study period. The "therapeutic period" for a treatment is the time from the first fill, to the date of the last fill plus the last days supply. "Combination Therapy" is defined as two treatments overlapping by a minimum of 90 days. A "switch" in therapy is defined as a change from one treatment to another where there is no more than a 90 day gap in therapy, and no more than 90 days of overlap in therapy. A "gap" in treatment is defined as a period of 90 days or more following the end of a therapeutic period, plus any days in the hospital (for non-mental health reasons). Studies have typically used periods of 30 to 90 days to define gaps in therapy [27, 28, 30]. This study utilized the 90 day period to match the longest days supply likely to be received by patients.

Demographic variables were cleaned and defined as well. Individual's age was defined as the difference between their birth year, and the year 2000. There were no instances in the data where an individual had more than 1 gender on record. Employment and geographic variables were defined for each individual as the value that turned up most often for that individual (if more than one value was available).

Adherence was calculated utilizing the Medication Possession Ratio (MPR), calculated utilizing equation 1 below. Although a variety of methodologies for measuring adherence are available, several such as electronic

monitoring (MEMS caps), or patient questionnaires are not feasible. Although electronic monitoring is considered the gold standard [17], use of medical records or claims databases are considered more accurate than patient self-report. [17, 31, 32] The decision to use MPR rather than Proportion of Days Covered (PDC) was based on several studies supporting its use,[7, 13, 33, 34] as well as it being the most common measure reported in the literature, and therefore the best for comparison amongst studies. Individuals were defined as adherent to therapy if their MPR was above 80%.

Equation 1:

$$MPR = \frac{\left(\sum day\_qty\right) - last\_day\_qty}{Last\_fill\_date - First\_fill\_date}$$

Propensity Scores

Propensity scores were developed for the likelihood that a patient will be adherent given their demographic, clinical, and employment characteristics (see table III-2 for a list of specific variables). Chi-square analysis was conducted in order to identify key characteristics based on a p-value greater than 0.2. The full logistic regression model was then optimized using backwards stepwise regression. The log-likelihood test was used to determine if there were significant differences in the models. Correlations were utilized to identify risk of collinearity, and the Hosmer-Lemeshow test was used to assess goodness-of-fit.

Matching and Statistical Analysis

Individuals with an MPR greater than 80% were matched 1:1 to non-adherent individuals based on the propensity scores. A nearest neighbor matching algorithm was used, utilizing calipers set to ½ of a standard deviation of the propensity scores. Standardized differences were used to assess balance in variables before and after matching. This methodology is the same at that used by Bangelore et. al. [35] in their analysis of the impact of beta-blocker use on clinical outcomes. The difference in hospitalization risk between adherent and non-adherent individuals was also assessed using the Chi-square test. Logistic regression was also utilized to control for factors differing between the hospitalized and non-hospitalized populations following matching. This model was optimized and tested in the same manner as the propensity score models described above.

Results

Population:

This population examined in this study is described in table III-2. The mean age of the population was higher in the pre-match population than the post-match population (46.7 vs. 46.3) prior to matching, but the difference was not clinically significant. The population contained fewer males both before and after matching (41.2% pre, 39.9% post). The percent of individuals living in rural areas increased slightly from 19.1% to 19.6%, with a slight increase in the proportion of individuals living in the South and West. There were also slight increases in the number of full time and salaried workers. The number of individuals with other mental health conditions increased by about 4.2%, but other comorbidities remained similar. Overall, the matched group is representative of the population from which it was produced.

Propensity Scores:

The propensity score model was successfully optimized (see table III-3) based on changes in -2 log likelihood. Goodness-of-fit was adequate based on a c-statistic = 0.782, and Hosmer-Lemeshow p-value = 0.482. The key drivers of adherence based on this model were age, gender, region, anxiety, other mental health diagnoses, diabetes, full time employment, and salary vs. hourly pay.

There was support for matching adherent to non-adherent individuals across nearly the full range of assigned propensity scores (see figure III-2).

Matching:

Matching was successful in limiting the differences in key variables associated with adherence between the adherent and non-adherent populations. A match was identified for 76.5% of the adherent individuals, utilizing 91.6% of the non-adherent individuals. Figure III-3 describes the standardized differences in key variables before and after matching.

Prior to matching, age was significantly higher in the adherent population than the non-adherent population (47.7 vs. 45.5, p-0.002), but after matching the difference was no longer statistically significant (45.8 vs 46.9, p-0.169 in the adherent and non-adherent groups respectively). Differences between the adherent and non-adherent populations based on gender remained insignificant at the alpha = 0.05 level, as was the case for location and most of the comorbidities evaluated. There was a statistically significant difference before matching in other mental health disorders, which did not exist following matching. The variables that were significant at the alpha = 0.2 level prior to matching were also no longer significant after matching. Table III-2 provides the details of these results. The details of the model fitting procedure are provided in table III-3.

Impact of Adherence on Hospitalization:

The impact of adherence on hospitalization rates was apparent in the unmatched population, as well as the matched only and matched and statistically controlled groups. The relative risk of hospitalization in the matched non-adherent group was 55% higher than in the adherent population (RR 1.55, 95% CI 1.07 - 2.25). In the unmatched population, the relative risk of hospitalization in the non-adherent group was 74% higher than in the adherent population (RR 1.7441, 95% CI 1.22 - 2.49). Hospitalization rates in each group are described in table III-4.

There were also significant differences in a variety of clinical, demographic, and employment characteristics between hospitalized and non-hospitalized individuals both before and after matching. Table III-5 describes these characteristics in the hospitalized and non-hospitalized populations before and after matching. The strongest drivers of hospitalization in addition to adherence in both cases were comorbid bipolar disorder, anxiety, depression, and other mental health conditions, and therapy characteristics including choice of first vs. second generation antipsychotic, switching, and combination use.

After controlling for confounders using logistic regression, adherence was still a significant predictor of hospitalization avoidance (OR 0.627, 95% CI 0.394 - 0.999). Individuals with bipolar disorder, depression, and other mental health

conditions also had significantly higher rates of hospitalization. See table III-6 for model diagnostics, and table III-7 for odds ratios generated by the logistic model. The difference in hospitalization rates between users of first and second generation antipsychotics were not significant, but those who used combinations or switched therapies were significantly more likely to be hospitalized. Table III-8 describes the differences in hospitalization rates between the matched and un-matched populations, and table III-9 describes the differences in odds ratios between methods.

Discussion:

Poor adherence is a significant predictor of increased hospitalization risk for individuals with schizophrenia. This analysis clarifies the risk of non-adherence to therapy in a commercially insured population, and provides a clear incentive for patients, providers, caregivers, and insurers to ensure that those patients receiving antipsychotics remain true to their regimen. Identifying those individuals at risk for non-adherence and ensuring they are receiving support to overcome their barriers to adherence could lead to significantly lower numbers of hospitalizations, which in turn could lead to lower costs and essentially pay for the support programs.

Impact of adherence on hospitalizations

A variety of studies have looked at the association between adherence and hospitalizations due to mental health disorders, and many of them have found that hospitalization rates were nearly reduced by half between those who were adherent and those who were not.[19, 20, 36] This study found a more modest difference in hospitalization rates, with a relative risk of hospitalization of 1.55 (95% CI 1.07 – 2.25) in the non-adherent population, as compared to adherent populations. Although adherence to medication is an important factor in avoiding hospitalizations, several other key factors emerged as well, with comorbidities,

polypharmacy, and treatment switches increasing the likelihood of hospitalization.

The hospitalization rates seen in this population are below those seen in Medicaid populations[20] (42% in the Medicaid non-adherent population vs. 14.5% in the commercial non-adherent population). This reinforces the need for population specific studies, as the severity of disease in this population is significantly lower as measured by hospitalizations.

Meaning of different methodologies

The importance of properly controlling comorbidities was also evident after examining the results of this analysis. Although the same conclusion holds throughout the unmatched, matched, and matched with logistic regression analyses, the magnitude of the impact decreases significantly with stronger controls for selection bias and potential confounders. Many of the studies performed in the literature did not control as carefully for these biases, and may be over-estimating the impact of adherence on hospitalization rates. Although adherence is important in avoiding hospitalizations, inflating the impact may divert limited funds from managed care outreach programs that address polypharmacy and other therapeutic issues to those focused more directly on adherence. In the end, it would be ideal to address all of a patient's medication taking behaviors, but the statistical analysis in this study shows that getting

people settled on a suitable monotherapeutic regimen might result in a lower rate of hospitalizations.

Limitations

This study is limited to inferences that can be made from claims databases. A matched cohort study cannot be used to assess causality, although every attempt was made to address potential confounders, issues known to impact adherence and risk of hospitalization such as social support and disease severity could not be observed based on claims data. The limited timeframe of the study also made it difficult to assess the impact of persistence on outcomes. Users of depot medications were excluded from the study, potentially eliminating individuals with more severe, or long-term illness. The age of the data utilized in this study may also lead to limited generalizability due to changes in available therapies and differences in guidelines. The results are also limited in generalizability to the commercially insured population, and differ significantly for similar studies of Medicare, Medicaid, and Veterans populations.

Studies utilizing claims records to measure adherence are prone to several well documented limitations. For instance, without observing an individual taking a medication one cannot be sure that it is being taken. Pharmacy claims can also be incomplete if patients receive samples from their physician, or pay cash rather than their copay for inexpensive generics, resulting in underestimates of adherence. Severity of illness is also a confounder that is

difficult to control for based on claims data, but may have biased the results if individuals with more severe disease were also less likely to be adherent to therapy.

Conclusions

Regardless of methodology, there risk of hospitalization increases substantially if individuals are not adherent to therapy as prescribed. Although adherence is a significant issue, polypharmacy and switching between treatments are also closely tied to hospitalization, and future studies should assess their impact.

Figures:

Figure III-1: Inclusion and exclusion criteria flowchart

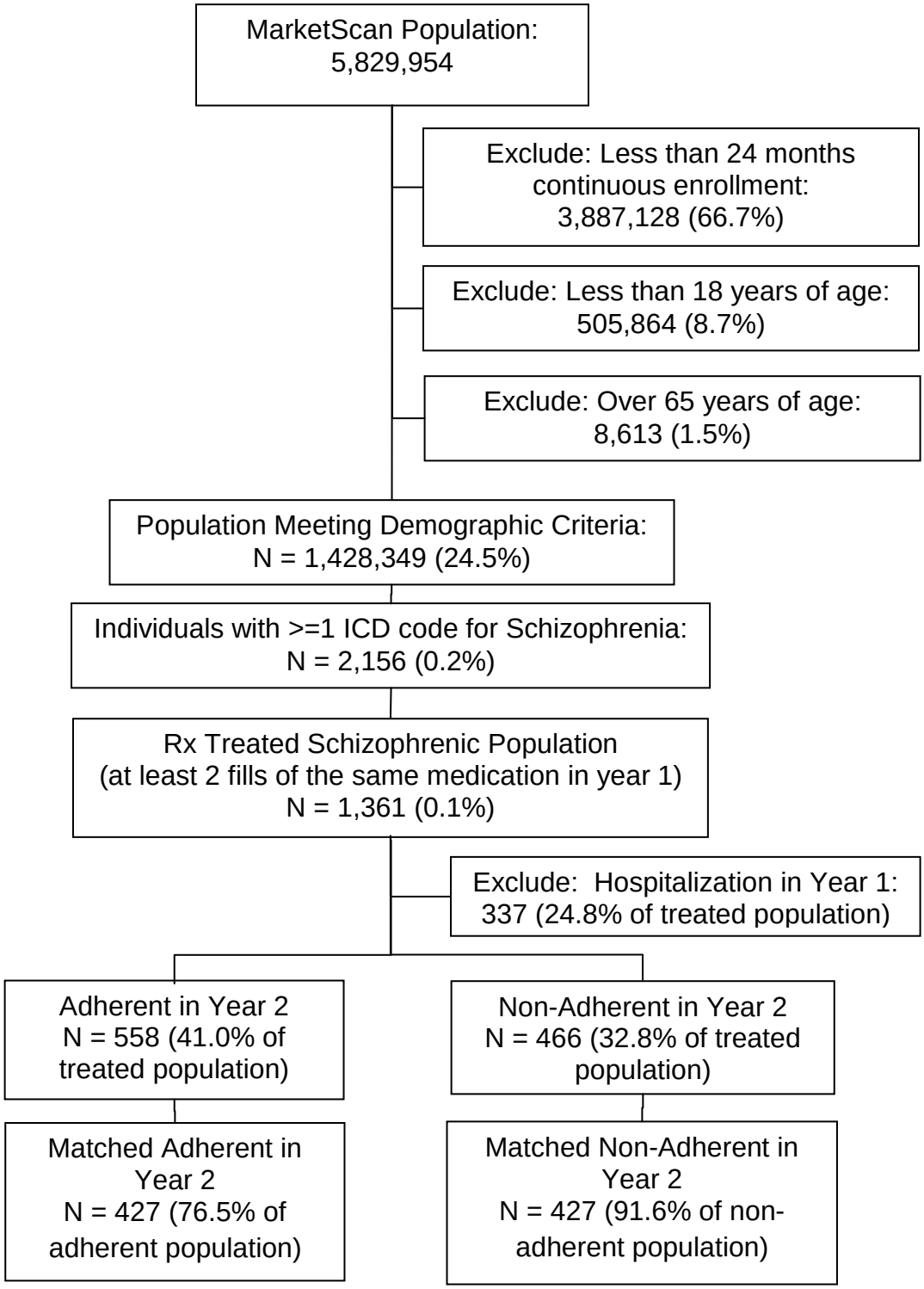


Figure III-2: Matching support for propensity scores in adherent vs. non-adherent populations

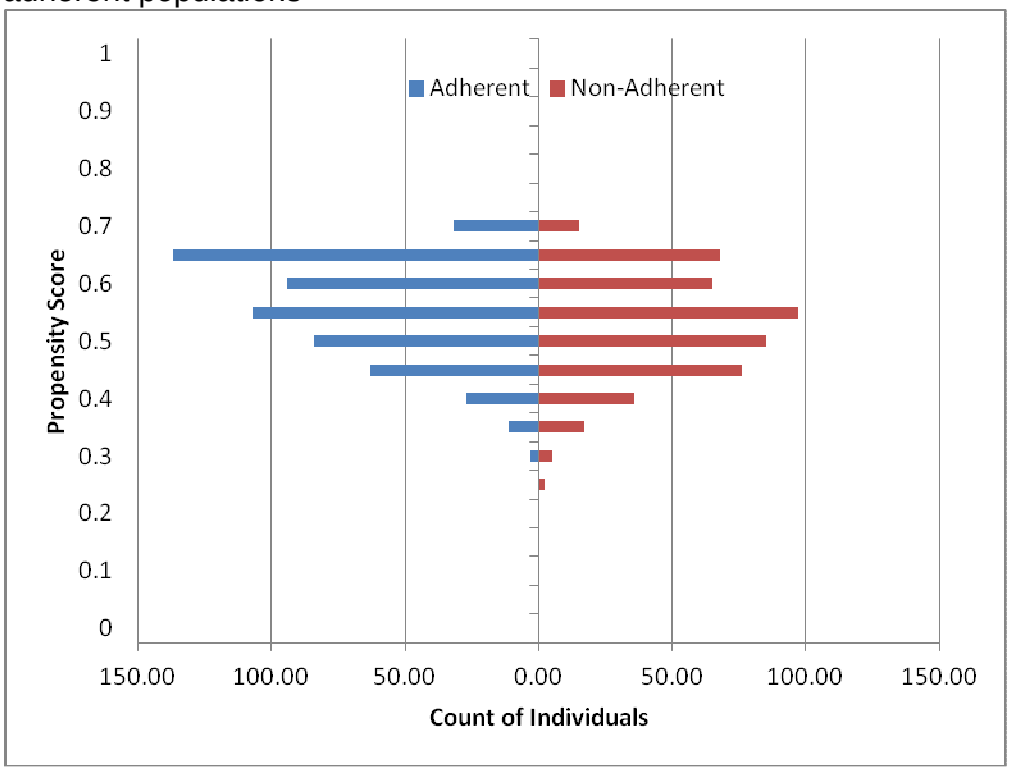
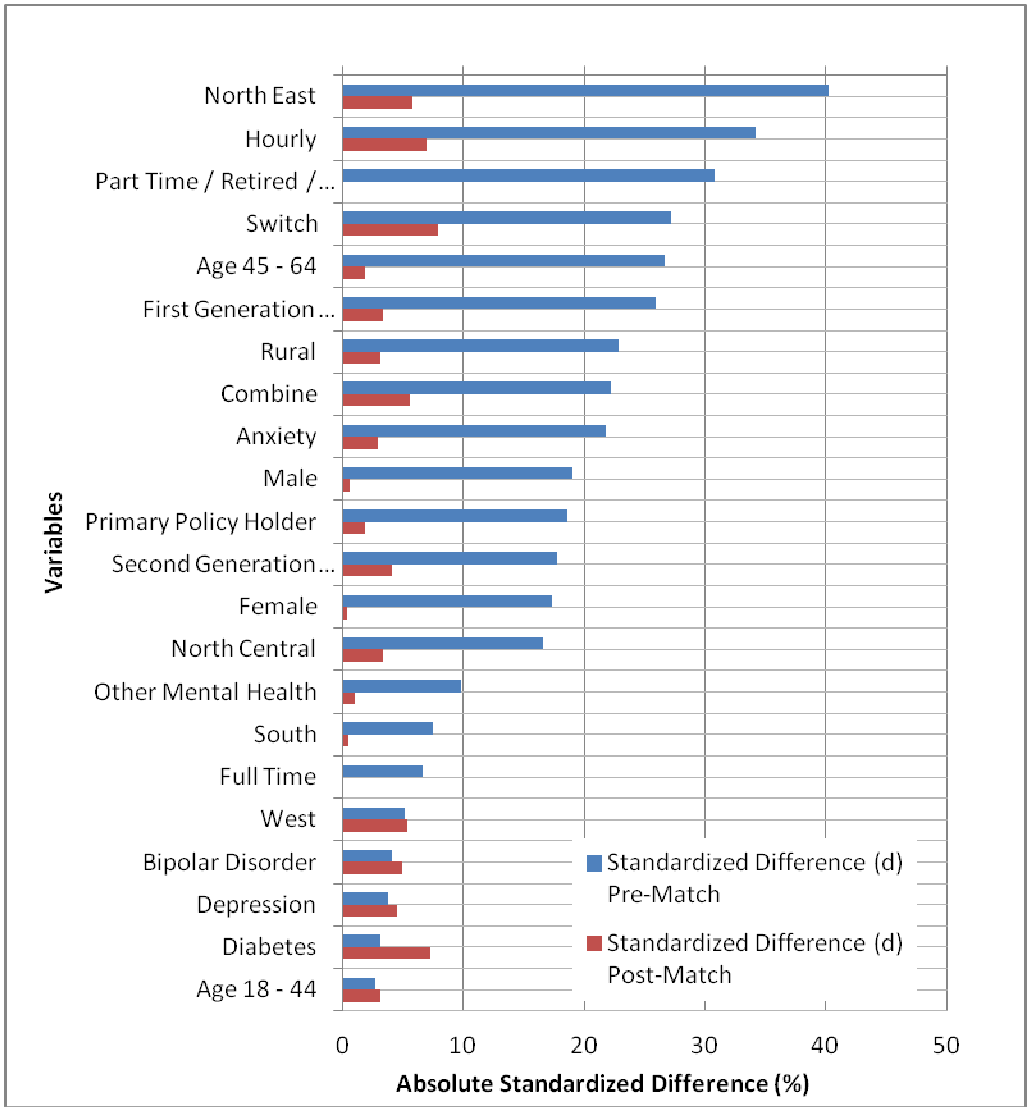


Figure III-3: Absolute standardized differences in matched variables before and after matching



Tables:

Table III-1: ICD-9 Codes used for identifying diagnoses with primary conditions and comorbidities

Condition	ICD-9 Codes Included
Schizophrenia	295 - 295.95
Bipolar Disorder	296 - 296.99
Anxiety	300 - 300.09
Depression	311, 300.4
Other Mental Health	290 - 319, except for those listed above
Diabetes	250.00 – 250.99

Table III-2: Bivariate analysis of clinical, demographic, and employment factors potentially associated with adherence before and after matching

		Pre-Match							Post Match						
		Total (N = 1024)		Adherent (N=558)		Non-Adherent (N = 466)		p-value	Total (N = 854)		Adherent (N=427)		Non-Adherent (N=427)		p-value
		N	% of Total	N	% Adherent	N	% Non-Adherent		N	% of Total	N	% Adherent	N	% Non-Adherent	
Age	18 - 44	367	35.8	186	50.7	181	49.3	0.067	319	37.4	157	49.2	162	50.8	0.784
	45 - 64	657	64.2	372	56.6	285	43.4		535	62.6	270	50.5	265	49.5	
Gender	Male	422	41.2	231	54.7	191	45.3	0.894	341	39.9	171	50.1	170	49.9	0.944
	Female	602	58.8	327	54.3	275	45.7		513	60.1	256	49.9	257	50.1	
Location	Rural	196	19.1	97	49.5	99	50.5	0.118	167	19.6	78	46.7	89	53.3	0.343
	Non-Rural	828	80.9	461	55.7	367	44.3		687	80.4	349	50.8	338	49.2	
	North East	269	26.3	161	59.9	108	40.1	0.144	206	24.1	106	51.5	100	48.5	0.965
	North Central	290	28.3	157	54.1	133	45.9		240	28.1	118	49.2	122	50.8	
	South	424	41.4	220	51.9	204	48.1		371	43.4	185	49.9	186	50.1	
	West	39	3.8	20	51.3	19	48.7		37	4.3	18	48.6	19	51.4	
Diagnoses	Bipolar Disorder	241	23.5	123	51.0	118	49.0	0.218	201	23.5	98	48.8	103	51.2	0.687
	No Bipolar Disorder	783	76.5	435	55.6	348	44.4		653	76.5	329	50.4	324	49.6	
	Anxiety	83	8.1	37	44.6	46	55.4	0.059	67	7.8	33	49.3	34	50.7	0.899
	No Anxiety	941	91.9	521	55.4	420	44.6		787	92.2	394	50.1	393	49.9	
	Depression	159	15.5	81	50.9	78	49.1	0.328	131	15.3	64	48.9	67	51.1	0.776
	No Depression	865	84.5	477	55.1	388	44.9		723	84.7	363	50.2	360	49.8	
	Other Mental Health	427	41.7	203	47.5	224	52.5	0.000	392	45.9	197	50.3	195	49.7	0.891
	No Other Mental Health	597	58.3	355	59.5	242	40.5		462	54.1	230	49.8	232	50.2	
	Diabetes	189	18.5	93	49.2	96	50.8	0.106	164	19.2	79	48.2	85	51.8	0.602
	No Diabetes	833	81.3	463	55.6	370	44.4		690	80.8	348	50.4	342	49.6	
Medication Utilization	Second Generation Antipsychotic	645	63.0	351	54.4	294	45.6	0.491	541	63.3	276	51.0	265	49.0	0.201
	First Generation Antipsychotic	280	27.3	158	56.4	122	43.6		236	27.6	120	50.8	116	49.2	
	Both (Combination)	99	9.7	49	49.5	50	50.5		77	9.0	31	40.3	46	59.7	
	Switched To	238	23.2	112	47.1	126	52.9	0.009	200	23.4	87	43.5	113	56.5	0.036
	Not post switch	786	76.8	446	56.7	340	43.3		654	76.6	340	52.0	314	48.0	
	Combined	165	16.1	81	49.1	84	50.9	0.128	134	15.7	57	42.5	77	57.5	0.060
	Not Combined	859	83.9	477	55.5	382	44.5		720	84.3	370	51.4	350	48.6	
Employment	Full Time	538	52.5	278	51.7	260	48.3	0.057	464	54.3	232	50.0	232	50.0	1.000
	Part Time / Retired / Unemployed	486	47.5	280	57.6	206	42.4		390	45.7	195	50.0	195	50.0	
	Primary Policy Holder	507	49.5	277	54.6	230	45.4	0.928	414	48.5	205	49.5	209	50.5	0.784
	Dependent	517	50.5	281	54.4	236	45.6		440	51.5	222	50.5	218	49.5	
	Salary	209	20.4	102	48.8	107	51.2	0.107	184	21.5	94	51.1	90	48.9	0.707
	Hourly	279	27.2	163	58.4	116	41.6		230	26.9	119	51.7	111	48.3	
	No Pay / Unknown	536	52.3	293	54.7	243	45.3		440	51.5	214	48.6	226	51.4	

Table III-3: Model fitting diagnostics for propensity score, modeling likelihood of hospitalization among adherent and non-adherent groups, controlling for other covariates.

Iteration	Description	Log Likelihood	Difference in -2 Log Likelihood	Model DF	critical value (x^2)	P-value
1	Full Model*	1376.41		11		
2	Full Model - Rural**	1377.705	2.59	10	3.84	>0.05
3	Full Model - Rural, Anxiety	1379.704	3.998	9	3.84	<0.05

*Full model Includes: Age, gender, rural, region, anxiety, other mental health diagnosis, diabetes, and full time employment and salary vs. hourly pay
**Final model includes all variables from the full model except rural

Table III-4: Hospitalization rates in the adherent and non-adherent populations before and after matching

	% Hospitalized	
	Un-Matched	**Matched**
Adherent	8.2	9.4
Non-Adherent	14.38	14.5
Relative Risk	1.74	1.55
95% CI for RR	1.22 - 2.49	1.07 - 2.25

Table III-5: Demographic, clinical, and employment characteristics in the hospitalized and non-hospitalized populations before and after matching

		Pre-Match					Post Match				
		Hospitalized (N=113)		Non-Hospitalized (N = 911)		p-value	Hospitalized (N=102)		Non-Hospitalized (N=752)		p-value
		N	% Hospitalized	N	% Non-Hospitalized		N	% Hospitalize	N	% Non-Hospitalized	
Age	18 - 44	54	14.7	313	85.3	0.005	47	14.7	272	85.3	0.052
	45 - 64	59	9.0	598	91.0		55	10.3	480	89.7	
Gender	Male	43	10.2	379	89.8	0.470	36	10.6	305	89.4	0.308
	Female	70	11.6	532	88.4		66	12.9	447	87.1	
Location	Rural	17	8.7	179	91.3	0.241	14	8.4	153	91.6	0.114
	Non-Rural	96	11.6	732	88.4		88	12.8	599	87.2	
	North East	26	9.7	243	90.3	0.589	24	11.7	182	88.3	0.887
	North Central	38	13.1	252	86.9		32	13.3	208	86.7	
	South	45	10.6	379	89.4		42	11.3	329	88.7	
	West	4	9.8	37	90.2		4	10.8	33	89.2	
Diagnoses	Bipolar Disorder	62	25.7	179	74.3	<0.0001	55	27.4	146	72.6	<0.0001
	No Bipolar Disorder	51	6.5	732	93.5		47	7.2	606	92.8	
	Anxiety	14	16.9	69	83.1	0.077	12	17.9	55	82.1	0.117
	No Anxiety	99	10.5	842	89.5		90	11.4	697	88.6	
	Depression	39	24.5	120	75.5	<0.0001	33	25.2	98	74.8	<0.0001
	No Depression	74	8.6	791	91.4		69	9.5	654	90.5	
	Other Mental Health	86	20.1	341	79.9	<0.0001	80	20.4	312	79.6	<0.0001
	No Other Mental Health	27	4.5	570	95.5		22	4.8	440	95.2	
	Diabetes	23	12.2	166	87.8	0.582	21	12.8	143	87.2	0.705
	No Diabetes	90	10.8	745	89.2		81	11.7	609	88.3	
Medication Utilization	Second Generation Antipsychotic	80	12.4	565	87.6	0.0001	73	13.5	468	86.5	0.0012
	First Generation Antipsychotic	14	5.0	266	95.0		15	6.3	222	93.7	
	Both (Combination)	19	19.2	80	80.8		14	18.4	62	81.6	
	Switched To	48	20.2	190	79.8	<0.0001	43	21.5	157	78.5	<0.0001
	Not post switch	65	8.3	721	91.7		59	9.0	595	91.0	
	Combined	30	18.2	135	81.8	0.001	25	18.7	109	81.3	0.009
	Not Combined	83	9.7	776	90.3		77	10.7	643	89.3	
Employment	Full Time	63	11.7	475	88.3	0.468	56	12.1	408	87.9	0.902
	Part Time / Retired / Unemployed	50	10.3	436	89.7		46	11.8	344	88.2	
	Primary Policy Holder	48	9.5	459	90.5	0.113	42	10.1	372	89.9	0.116
	Dependent	65	12.6	452	87.4		60	13.6	380	86.4	
	Salary	27	12.9	182	87.1	0.448	24	13.0	160	87.0	0.558
	Hourly	26	9.3	253	90.7		23	10.0	207	90.0	
	No Pay / Unknown	60	11.2	476	88.8		55	12.5	385	87.5	

Table III-6: Model fitting diagnostics for the likelihood of hospitalization, modeling the likelihood of hospitalization among adherent and non-adherent groups, controlling for other covariates following within the matched population

Iteration	Description	Log Likelihood	Difference in -2 Log Likelihood	Model DF	Critical Value (x^2)	P-value
1	Full Model*	498.14		13		
2	Full Model - Anxiety	498.154	0.028	12	3.84	>0.05
3	Full Model - Anxiety, Comb	498.366	0.424	11	3.84	>0.05
4	Full Model - Anxiety, Comb, Rural**	499.658	2.584	10	3.84	>0.05
5	Full Model - Anxiety, Comb, Rural, Atyp	508.198	17.08	9	3.84	<0.05

*Full model Includes: Adherence, Age, gender, rural, bipolar, anxiety, depression, other mental health diagnosis, atypical use, combination, switching, and primary coverage
**Final model includes all variables from the full model except anxiety, combination use, and rural location

Table III-7: Odds ratios for the likelihood of hospitalization

		Point Estimate	95%Confidence Limits	
Adherence	Adherent vs. non-adherent	0.627	0.394	0.999
Demographic	Male vs. Female	0.826	0.506	1.346
	Over 45 vs. Under 45	0.769	0.470	1.260
Clinical	Bipolar vs. No Bipolar	3.673	2.311	5.840
	Depression vs. No Depression	2.285	1.363	3.832
	Other Mental Health vs. None	3.511	2.064	5.972
	SGA vs. FGA	1.764	0.915	3.401
	FGA / SGA Combo vs. FGA	3.910	1.628	9.388
	Switch vs. no switch	2.138	1.329	3.441
Employment	Responsible for coverage vs. Dependent	0.626	0.388	1.010

Table III-8: Hospitalization rates in the adherent and non-adherent populations before and after matching

	% Hospitalized	
	Un-Matched	**Matched**
Adherent	8.2	9.4
Non-Adherent	14.38	14.5
Relative Risk	1.74	1.55
95% CI for RR	1.22 - 2.49	1.07 - 2.25

Table III-9: Odds of hospitalization in the unmatched, matched, and matched with logistic regression

	% Hospitalized		
	Un-Matched	**Matched**	**Match w/ Statistical Model**
Odds Ratio	0.535	0.609	0.627
p-value	0.0018	0.0203	0.0493
95% CI for OR	0.36 - 0.80	0.40 - 0.93	0.39 - 0.999

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