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Adherence to Common Cardiovascular Medications in Patients with Schizophrenia vs. Patients without Psychiatric Illness

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Abstract

Objective—The purpose of the study was to examine whether individuals with diagnoses of schizophrenia were differentially adherent to their Statin or angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB) medications compared to individuals without psychiatric illness.

Method—Using electronic medical record data across 13 Mental Health Research Network sites, individuals with diagnoses of schizophrenia or schizoaffective disorder receiving two or more medication dispensings of a statin or an ACEI/ARB in 2011 (N=710) were identified and matched on age, sex and Medicare status to controls with no documented mental illness and two or more medication dispensings of a statin in 2011 (N=710). Medication adherence, sociodemographic and clinical characteristics of the study population were assessed.

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Results—Multivariable models indicated that having a schizophrenia diagnosis was associated with increased odds of statin medication adherence; the odds ratio suggested a small effect. After adjustment for medication regimen, schizophrenia no longer showed an association with statin adherence. Having a schizophrenia diagnosis was not associated with ACEI/ARB medication adherence.

Conclusions—Compared to patients without any psychiatric illness, individuals with schizophrenia were marginally more likely to be adherent to their statin medications. Given that patterns of adherence to cardioprotective medications may be different from patterns of adherence to antipsychotic medications, improving adherence to the former may require unique intervention strategies.

Keywords

serious mental illness; schizophrenia; medication adherence; cardiovascular medications

1. INTRODUCTION

Schizophrenia is a chronic, serious mental illness (SMI) characterized by psychosis, hallucinations, delusions or disorganized speech and behavior. Approximately 2.4 million adults (1.1%) in the United States (U.S.) have schizophrenia in any given year [1]. The mortality rate among individuals with schizophrenia is two- to four-times greater than in the general population, due in part to higher rates of chronic disease such as cardiovascular disease, diabetes mellitus, hypertension and hyperlipidemia [2–4]. Higher rates of behavioral risk factors such as smoking [5], sedentary lifestyle [6] and poor dietary habits [6] as well as insufficient medical care [7] coupled with antipsychotic medication use (linked to metabolic problems including obesity, diabetes, dyslipidemia, and cardiovascular disease) [8, 9] contribute to early morbidity and mortality. Thus, personal (behavior, disease states, medication adherence), health care (utilization, medication prescription), and environmental (shelter, safety, etc.) factors all contribute to mortality in the underlying conceptual model.

Another possible explanation for higher mortality rate among individuals with schizophrenia, compared to the general population, may be that they are less likely to be adherent to prescribed medications compared to individuals without psychiatric conditions [10]. For example, prior research suggests that non-adherence to oral antipsychotic medications may be extremely common; some reports indicate that approximately 50% of individuals with schizophrenia do not take antipsychotic medications as prescribed [11–13]. Non-adherence to antipsychotic medications can have profound health implications, as evidence suggests that deviations from treatment can result in psychotic relapse, emergency department visits, and rehospitalization [14, 15]. Moreover, medication non-adherence may not be limited to antipsychotics; evidence suggests that non-adherence among individuals with schizophrenia is also problematic for other classes of medications, including those for hypertension and hyperlipidemia [16]. For example, Piette and colleagues found that patients with schizophrenia had poorer adherence to their hypoglycemic and antihypertensive regimens than to their antipsychotic medications [17]. Thus, non-adherence to these regimens could impact mortality via its effect on cardiovascular risk factor control. Few studies, however, have specifically compared rates of non-psychiatric medication

adherence between persons with versus without psychotic disorders; the studies that have been published thus far report mixed results. For example, three studies suggest that individuals with a diagnosis of schizophrenia do not differ in their hypoglycemic medication adherence [10] or anti-hypertensive medication adherence [18, 19] from those without any psychiatric illness. By contrast, another study reported that individuals with schizophrenia were more likely to be adherent to hypoglycemic medications compared to those without schizophrenia [20]. These studies were limited by small sample sizes or were conducted among military veterans within the Veterans Health Administration system. Thus, findings may not be generalizable to non-veteran populations because patients eligible for care in the Veterans Administration tend to be sicker and poorer than other veterans and United States residents in general [21]. Therefore, the purpose of the present study was to examine whether individuals with diagnoses of schizophrenia were differentially adherent to their anti-hyperlipidemic (statin) and/or anti-hypertensive (angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB) medications compared to individuals without any psychiatric illness. Analyses were completed using data from health care systems in the Mental Health Research Network and are representative of a large, geographically and racially/ethnically diverse population across the U.S.

2. MATERIAL AND METHODS

2.1 Overview

The Mental Health Research Network (MHRN) is a consortium of research centers located within 13 large health care systems, many of which also have affiliated health insurance plans. These integrated payer-provider systems are part of the larger Health Care Systems Research Network (HCSRN) formerly known as the Health Maintenance Organization Research Network (HMORN), which includes 17 U.S.-based health system members. MHRN-participating health systems serve over 12.5 million individuals across 15 states with diverse populations. All HSCRN sites maintain a Virtual Data Warehouse (VDW) consisting of electronic medical record (EMR) and insurance claim data for all of their enrolled HMO members or patients. Data on encounters, pharmacy fills, diagnoses, medical tests, demographics, and costs are organized using the same definitions across sites and are quality checked locally [22].

The current study involved seven MHRN systems. These sites were: Group Health Cooperative (Washington), HealthPartners (Minnesota), Henry Ford Health System (Michigan), Scott & White Healthcare (Texas), Kaiser Permanente Georgia, Kaiser Permanente Hawaii, and Kaiser Permanente Northwest (Oregon). Institutional Review Boards at each site approved data use for this project.

2.2 Study Sample

Cases were defined as follows: adults age 18–70 (at least 18 years by January 1, 2010) with schizophrenia (ICD-9 295.0–295.4, 295.6, 295.8–295.9) or schizoaffective disorder (ICD-9 295.7) diagnosed on at least 2 dates (one of which had to occur in 2010) during a mental health care encounter or by a mental health care provider, and receiving two or more medication dispensings of either a statin or an ACEI/ARB in 2011 (N=710). Eligible

individuals had to have continuous health plan membership throughout the observation period (but could have a gap in enrollment records of 30 days). Two or more fills of *any* statin or an ACEI/ARB were included, as clinicians may try different medications within a drug class while seeking a particular patient's optimal response. Typically, once patients are prescribed medication for diabetes and/or hypertension, providers may change the medication but rarely decide to discontinue that medication altogether. Therefore, consistent with approaches used in prior research [17], we assumed that patients should be refilling the medication throughout the observation period.

Controls were identified using the same criteria as described above except that they had no documented mental illness diagnoses during 2010 (N=710). Cases were matched on age, sex and Medicare status using stratified random sampling. It was not possible to match on Medicaid status as not all study sites enroll Medicaid members.

2.3 Measures

Medication adherence was assessed using Medication Possession Ratio (MPR), a measure of the proportion of time that an individual has medication available for use. It is calculated by dividing the sum of the days' supply of a medication obtained over an observation period by the days' supply needed if the patient were taking a full dose of the medication continuously during the observation period. The start of the observation period in the present study was the date of the first medication dispensing in 2011 and the end of the observation period was December 31st, 2011 or until the medication was discontinued by the provider. We considered an MPR of 0.80 adherent, consistent with other studies [23, 24]. If an individual was taking both a statin and an ACEI/ARB, his/her adherence was calculated separately for each.

We also examined sociodemographic (age, sex, race/ethnicity, neighborhood socioeconomic status) and clinical characteristics of the study population using data from 2010–2011. Age, sex and race/ethnicity were ascertained based on data available in the EMR as of 1/1/2011. Low neighborhood socioeconomic status was defined as having >20% of households below federal poverty level, calculated using patient addresses as of 1/1/2011 and census block data from the 2000 census. Uncontrolled systolic blood pressure (SBP) was defined as having at least two readings on different dates of a SBP >140 mmHg, and uncontrolled LDL cholesterol was defined as having an average LDL of >130 mg/dL. Both SPB and LDL data were calculated using the average of any recorded readings during 2010 and 2011. Body mass index (BMI) identified patients who were overweight (BMI of 25–29.9) or obese (BMI of 30+); data were calculated using the average of any recorded assessment during 2010 and 2011. Overall medical comorbidity burden was calculated using the Charlson Comorbidity Index Score (CCIS). This score contains 19 categories of comorbidity, with each category weighted based on the adjusted risk of 1-year post-discharge mortality. The overall comorbidity score reflects the cumulative increased likelihood of 1-year mortality; the higher the score, the more severe the burden of comorbidity [25]. CCIS data were calculated using data from 2010. The complexity of an individual's medication regimen was calculated by obtaining the number of American Society of Health-System Pharmacists (AHFS) medication groups filled during 2011. Healthcare utilization (hospitalizations, emergency

department [ED] visits and other in-person outpatient encounters) were based on summarized data from the last 6 months of 2011. Because we were interested in counting utilization days, multiple outpatient encounters documented on the same day were counted only once.

Preliminary data comparisons across sites were made by the study team to investigate site variation and to ensure accuracy of the data before creating aggregated estimates. This preliminary comparison found very little site variation, supporting the stability of the aggregated estimates.

2.4 Analyses

The primary goals of our analyses were to examine whether having a diagnosis of schizophrenia or schizoaffective disorder was associated with statin or an ACEI/ARB medication adherence as well as to estimate the effect of other patient-specific covariates on adherence. For initial bivariate models, we used t-tests for continuous variables and Pearson chi-square tests for categorical data. Although patients were matched on age category, mean age differed (see results), and thus age was controlled for in subsequent analyses. We fit multivariable logistic regression models in which MPRs >0.80 were used as primary outcome variables of interest. Results of the models were reported as adjusted odds ratios (OR) with 95% confidence intervals.

Three models were estimated. In model 1, we included schizophrenia diagnosis status as well as indicators of patients' sociodemographic characteristics as controls for confounding. In model 2, we included all variables in model 1 as well as measures of patients' clinical characteristics and health service use. In model 3, we included all previous variables as well as additional information about the complexity of patients' medication regimens. These variable blocks were selected based on previous literature which suggests that (1) clinical characteristics, (2) health service use and (3) medication regimens may be factors which are independently associated with adherence [17].

3. RESULTS

The sample of 1,420 patients included 33% of minority race/ethnicity, 12% living in low-income neighborhoods, 34% with uncontrolled hypertension, 13% with uncontrolled LDL cholesterol, 23% with an ED visit in the last 6 months of 2011, and 11% with a hospitalization during the same period. Patients ranged in age from 18 to 70 (mean 55.22, SD 9.7) and 44% were male. On average, patients were overweight or obese (36% had BMI of 30 or higher). Statin adherence averaged 56% among statin users. Bivariate analyses indicated that individuals with schizophrenia were more likely to have a higher body mass index, a higher Charlson comorbidity score, a greater number of medications filled, an ED visit or a hospitalization in the past 6 months and a higher frequency of outpatient visits compared to individuals without any psychiatric illness. Individuals with schizophrenia were less likely to have uncontrolled systolic blood pressure or uncontrolled LDL and more likely to have better statin adherence compared to individuals without any psychiatric illness (see Table 1).

Multivariable models indicated that having a schizophrenia diagnosis was associated with increased odds of statin medication adherence; the odds ratio suggested a small effect (less than 4:1/3:1 in the two models excluding medication regimen complexity). After adjustment for medication regimen, schizophrenia no longer showed an association with statin adherence (see Table 2). Having a schizophrenia diagnosis was not associated with ACEI/ARB adherence (see Table 3).

4. DISCUSSION

Compared to patients without any psychiatric illness, individuals with schizophrenia receiving treatment in integrated health care systems were more likely to be adherent to their statin medications (but not to their ACEI/ARB medications) despite having higher rates of medical comorbidities that have been previously shown to be independently associated with medication non-adherence. This finding is consistent with a study of U.S. military veterans that similarly reported that patients with psychotic disorders were more adherent to statins compared to those without any psychiatric illnesses [26]. By virtue of their greater mental health-related needs, and the known increased metabolic risk factors associated with antipsychotics, clinicians, family members and patients with schizophrenia may be paying greater attention to overall medical well-being as well as to potential medical consequences of psychiatric treatments [20]. Such enhanced awareness could lead to beneficial effects for patients with schizophrenia spectrum disorders. In addition, these disorders, like hyperlipidemia, are chronic conditions requiring long term, active self-care; thus, these patients may be well-practiced with day-to-day self-management tasks such as taking medications correctly and consistently. Alternatively, they may have well-activated caregivers ensuring their adherence to prescribed medications. It is also worth noting that study data are from integrated care settings where people with SMI may benefit most due to (1) the co-location of services such as primary care, laboratories, pharmacies, specialty care and (2) electronic medical record systems that facilitate coordination of this care. Further, because schizophrenia diagnosis was no longer significantly associated with statin adherence after controlling for a range of clinical, health service use and medication regimen characteristics, our findings suggests that these factors, including increased healthcare contacts, may be protective and facilitate adherence to some cardiovascular medications. Finally, while the confidence limit does include 1 in Model 3, we cannot exclude an odds ratio as high as 1.7; therefore, the non-significant effect of diagnosis should be interpreted with caution.

Interestingly, we found a positive association between emergency department visits and statin adherence among all participants. Many hospitals across the country – including some of those affiliated with the organizations participating in the present analysis – have implemented emergency room-based adherence interventions [27–44]. Thus, our participants may have been exposed to an intervention or new emergency room workflows aimed at increasing medication adherence, thereby leading to this positive relationship between ED visits and statin medication adherence. Patients without any psychiatric diagnosis did not differ from patients with a diagnosis of schizophrenia with respect to ACEI/ARB medication adherence. In their study using Medicare data from 1995–2003, Choudhry and colleagues reported that there have been statistically significant

improvements over time in patient medication adherence to statins but not to ACEIs/ARBs [45]. It is possible that, adherence to statins may be more sensitive to the myriad of clinical, health service and medication regimen characteristics, and consequently, more likely to vary across sub-populations such as those with versus without serious mental illness.

Despite our finding that individuals with schizophrenia were as or more likely to be adherent to their statin medications than individuals without any psychiatric illness, the overall rate of adherence for both groups was less than optimal (60% among individuals with schizophrenia and 52% among individuals without psychiatric illness). This is concerning given that non-adherence to cardioprotective medications (statins, beta-blockers and/or angiotension-converting enzyme inhibitors) has been associated with a 10–40% relative increase in risk of cardiovascular hospitalizations and a 50–80% relative increase in risk of mortality [46]. Thus, while there have been several interventions to date that have focused on improving adherence to *antipsychotic* medications among individuals with SMI [47], more studies are needed to evaluate whether these approaches are equally effective at promoting adherence to cardioprotective medications in this population. Given that patterns of adherence to cardioprotective medications may be different from patterns of adherence to antipsychotic medications [17], improving adherence to the former may require unique intervention strategies.

There are several limitations to our study that warrant mention. First, MPRs assess refill rates and thus may not necessarily represent patients' actual medication use. However, in a recent validation study that examined the predictive validity of eight different adherence measures among patients with schizophrenia, the MPR was recommended as one of the preferred adherence measures when a single measure is sought for use with administrative claims data [48]. Thus, we believe that we have sufficiently captured participants' medication adherence in these analyses. Second, analyses did not control for adherence to psychotropic medications nor for other cardioprotective drugs or drugs with cardiac risk. Third, this sample includes only people who filled at least two statin and/or ACEI/ARB prescriptions during the study period. Therefore, our analyses focus on adherence among those receiving *ongoing* treatment among established users and we did not examine primary non-adherence (failure to fill an initial prescription) or early non-adherence (discontinuing after a first prescription). It is possible that psychiatric illness may have a negative influence on adherence at those earlier stages. Surprisingly, there is a dearth of literature available that has assessed primary and/or early non-adherence in this population; in our review, most studies required at least 2 fills of the cardio-metabolic medication of interest [10, 16, 19, 26]. Therefore, more research is needed in this domain. Also worth exploring is the question about whether individuals with schizophrenia are less likely to receive *an initial prescription* for a statin, ACEI or ARB compared to individuals without any psychiatric illness. There is some evidence to suggest that providers may be less likely to treat other, unrelated health conditions among individuals with serious mental illness. For example, Redelmeier and colleagues reported that patients with psychotic syndromes were significantly less likely to receive treatment with both nonsteroidal anti-inflammatory agents and disease-modifying anti-rheumatic drugs compared with patients without psychotic syndromes; this effect persisted even after adjustment for age and sex. The researchers speculate that this finding

may be explained in three ways: (1) patients with chronic illness are already taxed and thus reluctant to accept additional treatments, (2) clinicians may want to keep treatment as simple as possible in order to avoid drug interactions and adverse events or (3) clinicians may be concerned that prescribing additional medications may alter a patient's adherence with current medications and indirectly cause harm [49]. Future research should explore whether individuals with serious mental illness are less likely to receive an initial prescription for cardio-metabolic medications compared with their counterparts without serious mental illness. Fourth, it is also important to note that healthcare utilization was assessed using data from the last 6 months of 2011 while medication adherence was assessed using all available data during 2011. Therefore, in some cases, our assessment of individuals' healthcare utilization may have not temporally occurred prior to our assessment of medication adherence. Finally, the findings are derived from a sample of members of integrated payer-provider systems. There is some evidence to suggest that individuals who are more economically and socially disadvantaged may be more severely ill [50]. Therefore, our largely insured sample may underrepresent the most impaired patients. Thus, caution is urged in generalizing the findings to uninsured or Medicaid populations. A future follow-up study could compare Medicaid to privately insured patients with serious mental illness to further explore whether differences exist between these populations with respect to medication adherence.

In spite of these limitations, this study has several strengths that include (1) a 12-month assessment period, (2) the use of an objective measurement of adherence, (3) the inclusion of possible covariates not assessed in prior studies [19] such as healthcare utilization, medical comorbidity and polypharmacy, and (4) the use of a large, geographically diverse sample. Future research should explore factors leading patients with schizophrenia demonstrating good cardiovascular medication adherence and develop interventions for patients with SMI with poor adherence.

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Table 1

Characteristics of the Study Population by Mental Diagnosis Category

Characteristic*	By Mental Diagnosis Category		Sig
	Schizophrenia Diagnosis	No Mental Health Disorder	
Race/Ethnicity (N=1,282)			
Non-Hispanic White	433 of 664 (65%)	425 of 618 (69%)	$\chi^2=23.54$, $p=0.002$
Non-Hispanic Black	114 of 664 (17%)	82 of 618 (13%)	
Asian/PI	49 of 664 (7%)	44 of 618 (7%)	
Hispanic	24 of 664 (4%)	15 of 618 (2%)	
Other	44 of 664 (7%)	52 of 618 (8%)	
Age	55.51 (SD=9.6)	56.46 (SD=9.4)	$t=2.00$, $p=0.05$
Male sex	316 (44%)	311 (44%)	$\chi^2=0.06$, $p=0.83$
Medicare	382 (54%)	383 (54%)	$\chi^2=0.01$, $p=0.96$
Low neighborhood SES	104 (15%)	72 (10%)	$\chi^2=6.51$, $p=0.01$
Body Mass Index (N=865)			
<24.9	48 (11%)	65 (16%)	$\chi^2=14.39$, $p=0.001$
25.0–29.9	109 (24%)	129 (31%)	
>30.0	295 (65%)	219 (53%)	
Uncontrolled Systolic Blood Pressure (N=1,013)	251 of 542 (46%)	232 of 471 (49%)	$\chi^2=3.70$, $p=0.03$
Uncontrolled LDL Cholesterol (N=860)	88 of 459 (19%)	96 of 401 (24%)	$\chi^2=2.79$, $p=0.01$
Medical comorbidity (Charlson Score)	1.33 (SD=1.5)	1.18 (SD=1.6)	$t=1.80$, $p=0.07$
Number of medications filled	7.77 (SD=4.3)	5.20 (SD=3.6)	$t=12.16$, $p<0.001$
Antipsychotic medication use (N=710)	659 (93%)	-	-
Any ER visits, past 6 months	214 (30%)	119 (17%)	$\chi^2=36.26$, $p<0.001$
Any Hospitalization, past 6 months	90 (13%)	62 (9%)	$\chi^2=6.09$, $p<0.001$
Average Number of outpatient clinic visits, past 6 months	12.5 (SD=12.0)	8.8 (SD=13.6)	$t=5.63$, $p<0.001$
Statin adherence among users (N=1107)	350 of 583 (60%)	271 of 524 (52%)	$\chi^2=8.25$, $p=0.004$
ACEI/ARB adherence among users (N=787)	232 of 383 (61%)	244 of 404 (60%)	$\chi^2=0.02$, $p=0.48$

* N=1,420 unless otherwise notated.

Table 2

Multivariable Analysis of Adherence to Statin Medications among Individuals with Vs. Without Psychiatric Illness (N=1,107)[†]

Characteristic	Model 1		Model 2		Model 3	
	Adjusted OR (CI)	P	Adjusted OR (CI)	P	Adjusted OR (CI)	P
Schizophrenia Diagnosis	1.46 (1.13–1.89)	0.004	1.58 (1.21–2.05)	0.001	1.29 (0.98–1.70)	NS
<u>Clinical and health service use characteristics</u>						
Medical comorbidity			1.13 (1.04–1.24)	0.01	1.02 (0.93–1.12)	NS
Any ER visits, past 6 mos			1.48 (1.07–2.07)	0.02	1.60 (1.13–2.25)	0.01
Any Hospitalization, past 6 mos			1.13 (0.72–1.79)	NS	1.38 (0.85–2.24)	NS
Number of outpatient clinic visits, past 6 mos			0.99 (0.98–1.00)	NS	0.98 (0.96–0.99)	0.001
<u>Medication regimen characteristics</u>						
Number of medications filled, past 6 mos					1.16 (1.11–1.21)	0.001

[†] Models also controlled for patients' demographic characteristics (age, neighborhood SES and race/ethnicity) and site.

Table 3

Multivariable Analysis of Adherence to ACEI/ARB Medications among Individuals with Vs. Without Psychiatric Illness (N=787)[†]

Characteristic	Model 1		Model 2		Model 3	
	Adjusted OR (CI)	P	Adjusted OR (CI)	P	Adjusted OR (CI)	P
Schizophrenia Diagnosis	0.98 (0.72–1.33)	NS	1.01 (0.74–1.38)	NS	0.79 (0.56–1.10)	NS
<u>Clinical and health service use characteristics</u>						
Medical comorbidity			0.98 (0.89–1.07)	NS	0.89 (0.81–0.99)	0.03
Any ER visits, past 6 mos			0.94 (0.64–1.37)	NS	0.89 (0.61–1.31)	NS
Any Hospitalization, past 6 mos			0.67 (0.41–1.10)	NS	0.56 (0.34–0.94)	0.03
Number of outpatient clinic visits, past 6 mos			1.00 (0.99–1.01)	NS	0.99 (0.98–1.00)	0.13
<u>Medication regimen characteristics</u>						
Number of medications filled, past 6 mos					1.12 (1.06–1.18)	0.001

[†] Models also controlled for patients' demographic characteristics (age, neighborhood SES and race/ethnicity) and site.