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MEDICATIONS ADHERENCE AND GLUCOSE CONTROL IN PATIENTS WITH PSYCHOTIC DISORDERS

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ABSTRACT

Objective: The aim of this research is to examine adherence, glycemic control and antihyperglycemic medication among individuals with schizophrenia and associated psychotic illnesses and a non-psychiatric control population. Methods: The medical records were reviewed retrospectively. Twenty-two diabetic patients with schizophrenia (31 patients with associated psychotic disorders, and 31 randomly chosen patients without psychiatric illnesses) getting medical care and psychiatric evaluation. Utilizing refill records from the system patient record , we calculated the cumulative mean gap ratio based on adherence to anti-hyperglycemic and anti-psychotic medication. To compare glycemic control between groups and to assess whether treatment guidelines for diabetes were meeting the glycemic goals, hemoglobin A1C values were utilized. Results: There were noticeable differences in adherence between the psychotic disorder group and the non-psychiatric comparison group when it came to anti-hyperglycemic medication, with approximately 65% of the psychotic disorder group missing anti-hyperglycemic medication for more than a month in the twelve month study period. Subject who adhere to their antipsychotic medications (80% adherent) were predominant to adhere to their antihyperglycemic medications (p=0.0003). Neither group differed significantly in glycemic control. Conclusion: Both groups had less than optimal adherence to antihyperglycemic medications and glycemic control. Psychotic patients and those without a mental illness did not show significant differences in adherence to antihyperglycemic medications and glycemic control.

Keywords: Mellitus, Psychotic disorders, Medication adherences.

INTRODUCTION

The non-adherence of schizophrenia patients to antipsychotic therapy is extensively studied because non-adherence can lead to bigger and expensive consequences such as relapses of psychosis, which can result in frequent clinic or emergency room visits and hospitalizations. According to a comprehensive review of the literature, 40-50% of antipsychotic users do not adhere to their medications. [2], Patients with psychotic illnesses are likely to experience nonadherence to antipsychotic therapy as well. When treating comorbid medical illnesses, it is important to examine medication adherence rates since, mostly occur in psychiatric patients, can be drug-induced, and have adverse long-term effects. A person with schizophrenia has two to four times the mortality rate of the general population. [4-6] Obesity, diabetes, and dyslipidemia are associated with antipsychotic medication treatment, particularly second-generation antipsychotics. [3] Some of the increased risk is due to suicide, but non-adherence to medication is also likely to be part of the reason, as well as inadequate care for chronic medical illnesses. Further justifies the need for studies in this area because schizophrenia patients can suffer from serious cognitive deficits and a lack of knowledge to their ailment and the requirement for treatment. As a consequence, nonadherence and negative outcomes of treatment are also more likely, further justifying the need for studies. [7]

There have been a number of studies conducted on patients with comorbid psychiatric illnesses and medication adherence for medical illness states such as diabetes,

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hyperlipidemia and hypertension. There is a 36-93% drop in compliance with diabetes medication regimens in patients without psychiatric illness. Psychiatric medication compliance rates were compared to those of medications for medical illnesses in a literature review published between 1975 and 1996. [9] Among those taking antipsychotics, 58% of the recommended number of medications were taken, while 65% of those taking an antidepressant and 76% of those receiving medical treatment took 58% of the recommended quantity of medications. There is evidence that psychiatric patients are less likely to adhere to their medication regimens than medical patients. In this study, medication adherence rates were compared for the first time between these populations, but caution should be exercised when interpreting the results because adherence rates were not measured in all studies cited.

The likelihood of patients adhering to their medication regimens is lower among psychiatric patients than among medical patients. A comparison of medication adherence rates between these populations was conducted for the first time in this study, but caution should be taken in interpreting the results, because not all studies reported adherence rates.[14-16] A patient's CMGR decreases as he or she becomes more adherent to prescribed therapy. Neither the compliant fill rate nor the CMGR significantly differed between medication classes after six or twelve months. There was a range of 52-64% in compliance rates over a twelve-month period. CMGR ranged from 5-15% over a twelve-month period, which translates into an average gap in therapy of 2-5 days a month. All medication classes experienced similar nonadherence rates. It was concluded that both antipsychotic and nonpsychiatric medication nonadherence rates were suboptimal in this study population. As a retrospective study, it had drawbacks like small sample size and retrospective design. Medication adherence in experts with diabetes and schizophrenia or hypertension was examined by Peitte and colleagues (n=1,686). [11] Medication possession ratios (MPRs) were calculated to assess adherence by dividing the number of days of medication given by the number of days needed. It was found that antipsychotic medication adherence was correlated with diabetes and hypertension drug therapy regimens. In a analysis adjusted for days' amount of medication dispensed, the adjusted odds for nonadherence was higher for anti-hyperglycemic (adjusted OR 1.5; $p<0.001$) and antihypertensive (adjusted OR 1.5; $p<0.001$) medications than anti-psychotic medication.

Researchers examined adherence to antihyperglycemic medication in patients getting treatment in the VA healthcare system who had schizophrenia (n=11,454) and without schizophrenia (n=10,560) [12]. Their findings showed a statistically big difference in medication compliance and blood pressure control between patients with age-matched controlsand schizophrenia. [13] During a year study, adherence rates were mean, reflecting approximately 30 days without antihypertensive medication ($p=0.71$). There is a particular study observing differences in a clinical outcome for a medical illness between patients who have and do not have a comorbid psychotic illness, even though it used a retrospective design and had a small sample size. It is recommended that further prospective studies be conducted between these patient groups to evaluate blood pressure control. Additionally, pilot data are needed to address the many common medical illnesses, including diabetes and hyperlipidemia, that have conflicting adherence information. The objective of our research was to relate difference between glycemic control and antihyperglycemic medication adherence and between outpatients with schizophrenia and age-matched individuals without psychiatric illness.

METHODS

Patient Selection

Annually, more than five million people receive primary and specialty care at approximately 100 medical centers and clinics. Medical, surgical, and mental health services are available in hospitals. Additionally, this medical center offers geriatric, neurological, cardiovascular, pneumology, psychiatric, gastroenterology, and oncology specialties. Computer databases identifying individuals prescribed an oral medicine to cure diabetes and hyperlipidemia were used to identify subjects. Inclusions were selected based on this criterion: During the study period, the patients who had two or more oral antihyperlipidemic prescriptions and antihyperglycemic (at least two months' worth of medication) were eligible; 2) the study included 4803 patients who were treated exclusively at primary care clinics for diabetes and hyperlipidemia. A study was not conducted on patients receiving insulin for Type I Diabetes. The subjects were divided into two study groups according to their characteristics a psychotic disorder is characterized by the following Individuals without a psychiatric diagnosis. The previous sample was analyzed to identify subjects taking an oral anti-psychotic medication during the same period. A total of 62 subjects were selected for inclusion: 1) who had filled at least two oral antipsychotic prescriptions during the 12-month study period; 2) who were under psychiatric care. We excluded patients who received a long-acting injectable antipsychotic as their primary treatment for psychosis. ICD-9 diagnostic codes for diabetes (ICD-9 code 250), hyperlipidemia (ICD-9 code 272) were verified on a computerized patient record system for both groups, and schizophrenia, schizoaffective disorder, or psychosis were used for the psychotic group. As well as identifying lack of psychiatric illness in the nonpsychiatric comparison group, this process was used to conduct the study. All inclusion criteria were met by 31 psychotic patients including diabetes, hyperlipidemia, and medication for psychosis. Study participants were all included. From the original pool, a random selection of age-matched individuals

without psychiatric illnesses was made. Participants in the study received the following antihyperglycemic drugs: Metformin, Glyburide, Glipizide), Rosiglitazone, and Pioglitazone. According to treatment guidelines, these medications are among the most commonly prescribed oral agents to treat diabetes and metformin is the most commonly prescribed medication in these classes. Study participants were identified based on all three antihyperglycemic medication classes. The study enrolled subjects who were receiving HMG-CoA reductase inhibitors, commonly referred to as statins. According to treatment guidelines, these are the most common antihyperlipidemic medications and represent the first line pharmacotherapy for hyperlipidemia. Identification of the original study sample was performed using a HMG-CoA reductase inhibitorA combination of fibrates, niacin, bile acid resins and ezetimibe was also collected if hyperlipidemia was being treated with combination therapy. Subjects were either treated with first-generation antipsychotics or second-generation antipsychotics in this study. Since both classes of antipsychotics are useful in treating schizophrenia, the original study sample was identified using both classes of medications. Those with hyperlipidemia and diabetes were in the study to reduce a potential confounder associated with a less aggressive approach to diabetes care. Diabetes-related outcomes are the only ones reported in our manuscript.

Data Collection

A review of digital medical records enabled us to gather demographic and clinical data, such as gender, body mass index, ethnicity, age, mental illness diagnoses and non-psychiatry diagnoses, duration of illness, smoking status, institutional encounters, and medication history. Each laboratory test also included an A1C measurement.

The CPRS was used to measure adherence to antihyperglycemic and antipsychotic medications. We assessed adherence rates for two parts of medications and for every medicine within a class for subjects receiving combination therapy for diabetes and/or psychosis. For adherence assessment, the medication with the highest nonadherence was selected when the subject took more than one diabetes or psychosis medication. CMGR [14] was used to assess medication adherence. Calculated by dividing the number of days during which medication was not consumed by the number of days during which it was consumed, the CMGR stands for daily medication consumption gap ratio. A CMGR ratio can be used to monitor gaps in treatment for antihyperglycemic and antipsychotic medications. A same method of assessing adherence has been implemented in previous studies on both psychiatric and nonpsychiatric medications [10,11,13]

Using A1C values and antihyperglycemic medication adherence rates, glycemic control was compared between groups. Based on these guidelines, glycemic control was determined by comparing A1C with treatment goals. A1Cs were compared with these guidelines' treatment goals to determine adequate glycemic control. Compared to their mean percentages of A1C measurements that met your goal, each subject's A1C measurements met the target goal.

Statistical Analysis

An interquartile range (IQR) was calculated for continuous variables based on mean, standard deviation, and standard deviation. Frequency and percentage were reported for categorical variables. Statistics were determined using bivariate analysis (e.g. Pearson's chi-square test, F test, t-test) for demographics and outcomes between treatment groups. Stata 9 was used to conduct the analysis. The p-value of 0.05 was used to determine the significance of the results.

RESULTS

Treatment Characteristics and Patients

Males dominated both groups, most of whom were obese, had hyperlipidemia, and suffered from two or more additional medical conditions aside from diabetes. Neither duration of diabetes, BMI, healthcare utilization nor medical comorbidities for medical needs were significantly different between the age-matched groups. Psychosis took up a higher percentage of blacks than nonpsychiatric patients in contrast to non-psychiatric patients. Among those suffering from psychosis, 37.1% were smokers compared to 14.5%. A statistically significant difference was also found between groups with psychosis and those without (p=0.002).

Schizophrenia constituted 67.7% of the psychosis group. Risperidone was prescribed by the majority of doctors (n=53; 85%), followed by ziprasidone (n=10; 18.9%). The subjects were also treated with olanzapine, quetiapine, and aripiprazole. Seven of the 18 (38.9%) subjects treated with a FGA in conjunction with a SGA received both treatments. A similar treatment regimen was prescribed for individuals taking antihyperglycemic medications. In terms of the use of combination therapy VS monotherapy, there were no difference between groups for the medication classes prescribed (biguanides, sulfonylureas, thiazolidinediones). Additionally, no significant differences were found for adherence among subjects based on the antihyperglycemic agent they were prescribed

Adherence

A cumulative mean gap ratio was calculated using metformin in 29.45% of the subjects, a sulfonylurea in 17.75%, and a thiazolidinedione in the remaining subjects. There were no significant differences between the psychosis and non-psychiatric groups in the CMGR for anti-hyperglycemic medications (p=0.181). Over the course of the 12-month period, the psychosis group had 58 days without medication and the nonpsychiatric comparison

group had 72 days without medication. Counting the number of days each subject has been on antihyperglycemic therapy for the calculation of antihyperglycemic adherence. The mean duration of evaluation for metformin and sulfonyl ureas (p=0.684) was not different between the two groups.

Over the course of a 12-month period, subjects who were suffering from psychosis had an antipsychotic CMGR of 9.15% (SD=8.2). This represents the average duration of assessment for the SGA for which the majority of the members were suffering from psychosis. Antipsychotic and antihyperglycemic medication adherence was significantly correlated for the psychosis group. The subjects who adhered to their antipsychotic therapy at 80% were more likely to adhere to their antihyperglycemic therapy (p=0.0003). According to the CMGR report, subjects adhering to anti-psychotics experienced an anti-hyperglycemic CMGR of 10.7% (SD=10.2), which indicates that they did not use anti-hyperglycemic medication for approximately 39 days throughout the 12-month study period. According to the antihyperglycemic CMGR, nonadherent participants who were on antipsychotics but not adhering had an adherence rate under 80%, indicating 97 days without diabetes medication.

Glycemic Control

Diabetes treatment goals were used to assess glycemic control in outpatient primary care clinics by measuring A1C using established diabetes treatment goals. [17] In table 2, glycemic control did not differ significantly between groups. Psychosis patients achieved a goal for A1C at all glycemic assessments than non-psychiatric patients (26.5%). One-third of the psychosis group subjects failed to achieve the A1C target of 7% throughout the study period in comparison with 8.85% of the non-psychiatric comparison group.

Table 1: Baseline Demographic Data and Clinical Characteristics of Psychosis and Non-psychiatric Comparison Subjects

Parameter	**Subjects without a psychiatric Illness (N=31)**	**Subjects with psychosis (N=31)**	**P-value**
Age (years), mean (SD)	29.6 (1.1)	28.95 (3.5)	0.150
Gender, N (%) Male	 31 (49.2)	 30 (48.4)	0.551
Ethnicity, N (%) White Black Other	 22 (34.7) 4 (6.4) 5 (17.7)	 7 (22.6) 11 (35.5) 6 (19.3)	 0.008
Body Mass Index (kg/m$^{2)}$, mean ± SD	17.5 ± 3.7	16.75 ± 3.15	0.441
Body Mass Index Classification[20], N (%) Underweight (BMI <18.5 kg/m^2) Normal weight (BMI 18.5-24.9 kg/m^2) Overweight (BMI 25-29.9 kg/m^2) Obesity Class I (BMI 30-34.9 kg/m^2) Obesity Class II (BMI 35-39.9 kg/m^2) Obesity Class III (BMI >40 kg/m^2)	 0 (0) 2 (2.4) 7 (11.3) 10 (16.9) 6 (9.7) 6 (9.7)	 0 (0) 2 (2.4) 9 (14.5) 9 (14.5) 7 (11.3) 4 (7.3)	 0.789
Duration of Diabetes (years), mean (SD)	2.61 (1.52)	3.71 (2.7)	0.080
Psychiatric Disorder, N (%) Schizophrenia Schizoaffective Disorder Psychosis, Not Otherwise Specified	 NA	 21 (33.81) 9 (14.5) 1 (1.6)	 NA
Comorbid Medical Diagnoses, N (%) Hyperlipidemia	 31 (50)	 62 (100)	 1.000
Hypertension	25 (40.3)	50 (80.6)	1.000
Coronary Artery Disease (CAD) or other CAD Risk Equivalent*	9 (14.5)	10 (16.1)	0.084
Total Comorbid Medical Diagnoses**, N (%)			0.651
1	3 (9.7)	2 (2.40)	
2	12 (40.3)	12 (19.31)	
3	12 (38.7)	13 (20.15)	
4	4 (11.3)	4 (8.1)	
Smoking, N (%)	4.5 (7.21)	11.5 (17.5)	0.003
Health Care Utilization, mean (SD)			
Primary Care Visits	3.2 (2.2)	2.5 (2.5)	0.208
Medical Emergency Room Visits	0.4 (1)	1.8 (2.8)	0.001
Psychiatric Emergency Room Visits	0	0.30	

Medical Hospitalizations	0.07 (0.26)	0.25 (0.65)	0.072
Psychiatric Hospitalizations	0	0.33 (1.2)	
Antihyperglycemic Medication Classes Prescribed, N (%) 1 Medication Class/Drug ≥ 2 Medication Class/Drugs	 16 (25.8) 15 (24.2)	 18 (29.05) 13 (20.91)	 0.469
Antihyperglycemic Medication Used for Adherence Calculation, N (%) Metformin Sulfonylurea Thiazolidinedione	 20 (31.41) 10(16.95) 1 (1.6)	 17 (17.4) 12 (16.5) 2 (4.05)	 0.832***
*Cardiovascular disease, peripheral arterial disease, and abdominal aortic aneurysms are other risk equivalents to Coronary Artery Disease (CAD) The Chronic Disease Score Instrument measures a person's comorbidity using pharmacy data, and includes the following disease states (peripheral artery disease ,CAD ,It includes abdominal aortic aneurysms, chronic obstructive pulmonary disease , Parkinson's disease , asthma, smoking, hypertension , rheumatoid arthritis, glaucoma, cancer, seizures, ulcers, and migraine headaches. Hyperlipidemia was also included in the total number of comorbidities. *** Metformin compared with all other antihyperglycemic drugs (thiazolidinedione or sulfonylurea)			

Table 2: Glycemic Control in Psychosis and Non-psychiatric Comparison Subjects

Parameter	**Subjects without a psychiatric illness (n=31)**	**Subjects with psychosis (n=31)**	**P-values**
Hemoglobin A1C - baseline, % mean (SD)	6.8 (1.6)	6.9 (1.3)	0.680
Hemoglobin A1C - final, % mean (SD)	7.0 (1.7)	7.1 (1.7)	0.795
Hemoglobin A1C – change from baseline to endpoint, % mean (SD)	0.21 (2.01)	0.11 (1.1)	0.581
Hemoglobin A1C <7% - final, N (%)	40 (66.1)	38 (60.3)	0.372
Hemoglobin A1C at goal, N (%)[17] 100% of assessments 75-99% of assessments 50-74% of assessments 25-49% of assessments 1-24% of assessments 0% of assessments	 16 (25.8) 1 (2.4) 6 (9.7) 2 (3.25) 0 (0) 6 (8.85)	 16 (16.6) 1 (1.6) 2 (3.7) 1 (1.6) 2 (3.21) 9 (13.7)	0.261

Figure 1: Antihyperglycemic Medication Adherence Psychosis and Non-psychiatric Comparison Subjects

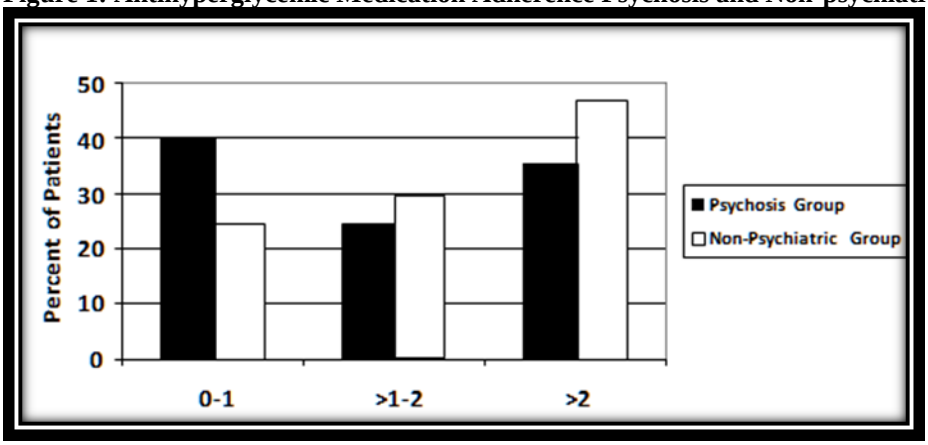
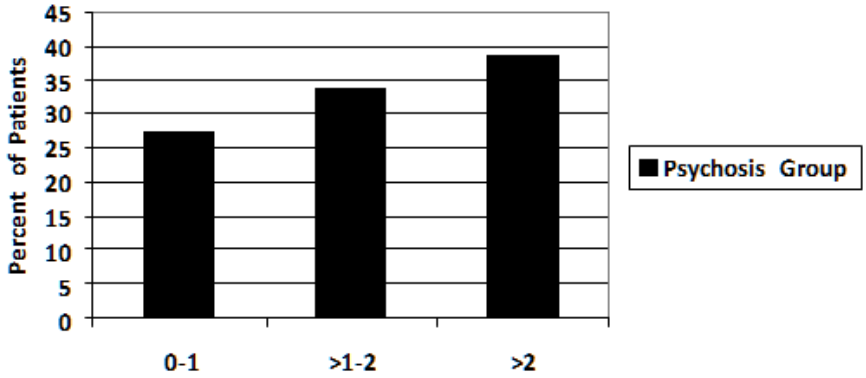


Figure 2: Antipsychotic Medication Adherence in Subjects with Psychosis



DISCUSSION

The compliance with oral antihyperglycemic agents and glycemic control of patients with psychosis were evaluated in our study. A significant difference was not found between groups in terms of antihyperglycemic medication adherence. The adherence of antihyperglycemic medications between these two patient populations was also compared in one study. Patients with schizophrenia were mostly to be affected by antihyperglycemic medications than patients without schizophrenia, but diabetics with schizophrenia were significantly less likely to abide by antihyperglycemic medications. The adherence rates for antipsychotics and antihyperglycemics did appear to be related in [12].

Researchers found no published studies that examined adherence to antihyperglycemic medications and control of blood sugar levels in chronic psychosis patients compared with a nonpsychiatric control group. This was the only research of its kind to focus on blood pressure control; Dolder and colleagues' study was the only one of its kind. As compared to an age-matched nonpsychiatric condition comparison group, blood pressure control was significantly lower in the psychosis group. Both groups adhered to their antihypertensive medications equally, however. As far as glycemic control was concerned, A1C values were almost identical between groups at baseline and at the end of the study. The lack of difference between groups on antihyperglycemic medication adherence and glucose control is surprising, despite several studies linking depression with poor diabetes control and non-adherence to antihyperglycemic medications. Schizophrenia is one of the most disabling psychiatric disorders because it causes a lack of insight and judgment, as well as cognitive deficits, similar to depression. The impact of mental illness in general, and particularly schizophrenia, on medical adherence as well as clinical outcomes is therefore likely to be negative. Furthermore, patients with psychiatric illnesses receive less quality diabetes care than those without. The results of our study agree with a growing body of literature showing that individuals with diabetes and psychiatric illnesses can receive adequate diabetes care, as well as those who do not have psychiatric illness receiving ongoing care. Both studies were conducted in VA healthcare settings, which directly relate to the study population. In spite of our finding that there were no significant differences between the groups, we found no significant differences in medication adherence between them. However, the psychosis group and nonpsychiatric comparison group both had lower medication adherence rates than optimal, with approximately 65% and 70% of patients not taking antihyperglycemic medications for more than 30 days over the last year, respectively. Psychosis patients had an A1C value over 9%, while only 13.5% of nonpsychiatric participants did. Nine percent and five percent, respectively, failed to achieve their A1C goal. As a result of fewer patients having poor glycemic control in commercial (28.4%), Medicare (29.4%), or Medicaid systems, compared to other insured populations, even though they had not reached their goals. Due to a higher level of healthcare utilization, the psychotic disorder group may have had higher adherence to medication. There was a significant difference between the subjects who visited the ER for medical reasons and the comparison group ($p=0.001$). In addition, psychotic disorders were associated with more medical hospitalizations ($p=0.073$). As a result of their mental illness, patients with psychotic disorders experienced additional healthcare interactions. Mental health services are required along with psychiatric emergency room visits and hospitalizations in most cases of schizophrenia and related psychotic disorders. Subjects with psychotic disorders received more care than subjects without these disorders, which suggests that they received more assistance. By interacting within the healthcare system, medication adherence could have been improved. Since our study has a retrospective design and a small sample size, its implications must be considered. As a result of strict inclusion criteria, only 31 subjects were included in the psychotic group within the specified timeframe. A small

sample size is another limitation of the study. As our study was restricted to a group of older, male patients within the VA healthcare system, our findings are likely not to apply to other segments of the US population. Further narrowing our study population was achieved by having strict inclusion criteria so that the nonpsychiatric control group and the psychosis comparison group were comparable demographically and in terms of treatment. As a healthcare system that focuses on outcomes and processes, diabetes care in the VA may differ from diabetes care in other healthcare settings. It may not be possible to generalize our findings to patients who take insulin therapy or injectable antipsychotics. Since the study was retrospective, medication adherence was not directly measured. Our indirect method of measuring adherence was based on refill rates calculated based on CMGR. In spite of the fact that refilling medications is objective and is correlated with other adherence behaviors, it may not accurately reflect medication use and consumption.

There are several strengths in our study, despite these limitations. The purpose of this study was to evaluate normal clinical practice. Refill records provided an accurate description of adherence in a naturalistic way without interfering with normal processes. The psychosis group was formed by including all patients who met criteria for the illness. Patients were not excluded for any reason (i.e. treatment resistance, history of nonadherence to medications, comorbid substance abuse/dependence). Additionally, we included only those patients whose medical and psychiatric care came from the VA healthcare system, excluded all psychiatric diagnoses from the comparison group that did not receive any psychiatric care, and only used A1C values obtained from primary care clinics to limit confounders. The outcome measures selected for this study are based on widely accepted diabetes treatment guidelines. Our study also has the advantage of a 12-month assessment period.

CONCLUSIONS

Participants with schizophrenia and related psychotic disorders had no significant differences in adherence to antihyperglycemic medications or glycemic control when compared with age-matched individuals without psychiatric illness. Neither group adhered to antihyperglycemic medications or controlled their blood glucose levels optimally. In addition to antipsychotic medication adherence, antihyperglycemic medication adherence was also significantly correlated. Research in this area should be conducted on a larger scale, involving replication in the VA healthcare system as well as in other non-VA community settings, as well as using several measures of adherence.

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