

# Adherence to Diabetes Medication in Individuals with Schizophrenia: A Systematic Review of Rates and Determinants of Adherence

Paul Gorczynski<sup>1</sup>, Hiren Patel<sup>2</sup>, Rohan Ganguli<sup>3</sup>

## Abstract

**Introduction:** Despite the importance of medication adherence for the effective treatment of type II diabetes mellitus (T2DM), little research has examined adherence with diabetes medication treatment in schizophrenia. The purpose of this systematic review was to: 1) evaluate rates of adherence and determinants of adherence with medication for T2DM in individuals with schizophrenia; and, where possible, 2) examine the relationship between medication adherence and glycemic control. **Methods:** Studies were included if they presented information on dosing regimens and adherence or compliance rates for T2DM and included samples where at least 50% of the participants were individuals with schizophrenia. **Results:** Six studies were included in this review that predominantly examined men over the age of 50 years. Studies confirmed that many individuals with schizophrenia were not adhering to their diabetes medication as adherence rates ranged from 51–85%. Two studies that compared medication adherence in individuals with and without schizophrenia found those with the mental illness had higher rates of adherence. One study reported that blood glucose control levels were not statistically different between those who did and did not adhere to their medication, indicating more research is necessary in this area. Factors that improved adherence included disease and medical service and medication-related factors. **Conclusions:** Interventions to increase diabetes medication adherence in schizophrenia need to address disease and medical service and medication-related factors. Further research needs to examine diabetes medication adherence in women, younger individuals, and those recently diagnosed with diabetes as these individuals have been underrepresented in the literature.

**Key Words:** Medication Adherence, Diabetes, Schizophrenia

<sup>1</sup>Department of Sport and Exercise Science, University of Portsmouth

<sup>2</sup>Institute of Medical Science, University of Toronto and Centre for Addiction and Mental Health

<sup>3</sup>Department of Psychiatry, University of Toronto and Centre for Addiction and Mental Health

Address for correspondence: Paul Gorczynski, University of Portsmouth, Department of Sport and Exercise Science, Spinnaker Building, Cambridge Road, Portsmouth, Hampshire, PO1 2ER, UK  
Phone: +44 23 9284 5175; E-mail: Paul.Gorczynski@port.ac.uk

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## Introduction

Individuals living with schizophrenia are at an increased risk of developing overweight or obesity (1). Low levels of physical activity, unhealthful diets, and certain antipsychotic medications (e.g., clozapine and olanzapine [2]) have been shown to be associated with excess body weight in this population (3-6). High rates of overweight and obesity in this population have been linked to increased rates of metabolic syndrome and chronic health conditions like type II diabetes mellitus (T2DM) (7, 8). Both obesity and T2DM have been

### Clinical Implications

This review illustrates that adherence to diabetes medication in schizophrenia is low and that complex interventions need to be constructed to address both modifiable and nonmodifiable determinants of diabetes medication adherence. Improving diabetes medication adherence is key to improving overall health in individuals with schizophrenia and reducing acute healthcare costs and utilization (38). This review also shows that other behaviors, considered cornerstones in overall diabetes care (60), such as exercise, diet, and blood glucose monitoring, have not been examined in individuals with schizophrenia with respect to medication adherence. Further research is needed to examine diabetes medication adherence in women, younger individuals, and those recently diagnosed with diabetes, as well as to explore behaviors commonly associated with improved medication adherence.

reported to be independent risk factors for cardiovascular disease (9), leading to a reduced quality of life and reduced life expectancy by approximately twenty-five years in people with this serious mental illness (1, 10-12).

In comparison to the general population, incidence of T2DM is two to four times higher in individuals with schizophrenia (2, 13, 14). High incidence of diabetes in schizophrenia has led to calls for action amongst practitioners who prescribe antipsychotic medication to begin metabolic monitoring programs when medication is first prescribed and at regular intervals thereafter to screen for metabolic abnormalities and take steps to prevent and, where necessary, treat diabetes (2, 15).

Effective treatment for diabetes often requires certain lifestyle modifications, such as increased physical activity, incorporating a healthful diet, and regularly checking blood glucose levels as well as taking diabetes medication (16). An essential component of treatment for diabetes in order to maintain glycemic control is medication adherence (17). Enhancing medication adherence has been shown to improve blood glucose levels and reduce overall complications associated with diabetes (18). The American Diabetes Association and Canadian Diabetes Association have recommended that all individuals diagnosed with diabetes receive self-management education in order to improve self-care practices and behaviors that contribute to optimal blood glucose control (19, 20). Researchers suggest that adherence with treatment, especially medication, for diabetes in the general population is low (21). Overall, people with schizophrenia have been shown to receive poorer diabetes care than those in the general population, including fewer tests that examine glycated hemoglobin (HbA1c) and serum lipid levels (22, 23). Research has also shown that individuals with schizophrenia are less likely to receive diabetes education (24), potentially impacting their ability to adhere to their medication regimens.

Despite the importance of medication adherence for the effective treatment of T2DM, little research has examined adherence with diabetes medication treatment in schizophrenia. The purpose of this systematic review was to: 1)

evaluate rates of adherence and determinants of adherence with medication for T2DM in individuals with schizophrenia; and, where possible, 2) examine the relationship between medication adherence and glycemic control.

### Method Inclusion and Exclusion Criteria

A methodology adapted from Cramer (21) and Peeters et al. (25) was used for this review. The review was carried out between May and November 2013. Studies were included in this review if they met the following criteria: 1) presented information on dosing regimens and adherence or compliance rates for T2DM; 2) described how adherence or compliance rates were calculated; 3) included samples where at least 50% of the participants were individuals with schizophrenia (any subtype, defined by the *Diagnostic and Statistical Manual for Mental Disorders-IV* [26]); and, 4) were written in English. No time limits were imposed for this review. For this review, *adherence* was defined as the “active, voluntary, and collaborative involvement of the patient in a mutually acceptable course of behavior to produce a therapeutic result” (27, 28). *Compliance* was defined as “the extent to which a person’s behavior coincides with medical advice” (27, 29). Studies were excluded from this review if they failed to discuss adherence or compliance information for T2DM and/or did not include a sample where the majority of the participants were diagnosed with schizophrenia or schizophrenia-like illness. For this review, the focus was T2DM and not type 1 diabetes because of lower rates of incidence of type 1 diabetes in schizophrenia than in the general population (30).

### Search Strategy

To identify studies, the following databases were searched: PubMed, CINAHL, PsychINFO, GOOGLE Scholar, and the Cochrane Library. Key search terms included “patient adherence,” “patient compliance,” “hypoglycemic agents,” “insulin,” “metformin,” “diabetes,” “diabetes mellitus,” “psychosis,” and “schizophrenia.” A hand search of the reference lists of reviews of the general literature and identified studies was also conducted.

## Analyses

Descriptive statistics are presented for the included studies, with information on the study author and year of publication, sample size, age, sex, diagnoses, setting and country, study type, medication type, measure of adherence, adherence, and glycemic control. Where necessary, additional information was obtained from one corresponding author. Factors associated with medication adherence are listed in one of four categories: 1) demographic; 2) psychological and cognitive factors; 3) disease and medical service factors; and, 4) medication factors. The methodology for reporting factors associated with medication adherence was adapted from exercise science literature used to report the determinants of physical activity in adults in the general population and those with schizophrenia (31-33). Each identified factor was listed as having a positive, negative, or no association with medication adherence. A simplified system of reporting associations between factors and medication adherence was used in this review given the different uni-, bi-, and multivariate analyses that were reported by each of the studies. Positive and negative associations were presented only if significant results between the factor and medication adherence were reported by the study. Null findings for factors were based on findings of nonsignificance.

## Results

A total of six studies met the inclusion criteria and were included in this review (34-39). Despite this review's focus on T2DM, no studies examining type 1 diabetes and medication adherence were encountered. Overall, sample sizes ranged from 44 to 33,230 participants, with three studies focusing mostly on men (34, 36, 37). The mean age of participants in all six studies was over 48 years (34-39). Two of the six studies compared diabetes medication adherence rates between individuals with and without diagnoses of schizophrenia and found better adherence in individuals with than in those without the mental illness (34, 35). All studies were conducted in the United States and involved retrospective assessments of medication use, with three studies relying on information obtained from Veterans Affairs databases (34, 36, 37). One study obtained self-report medication adherence information through interviews with participants (35). All studies examined adherence to oral hypoglycemic medication, while one study also examined injectable hypoglycemic medication (35).

Kreyenbuhl et al. (34) and Piette et al. (37) measured adherence using Medication Possession Ratios (MPR) (40-43). MPRs are calculated by dividing the total medication dispensed by the number of days supply needed for continuous care. An MPR of less than 80% was considered nonadher-

ent. Dolder et al. (36) used the Compliant Fill Rate (CFR) and the Cumulative Mean Gap Ratio (CMGR) (44, 45). CFR examines the number of total medication fills that are filled at appropriate time intervals over a specific period of time. Adherence is measured by comparing the number of days of medication supply with the number of calendar days between fills. An adherent fill is one that is completed before the next prescription and there is no more than 20% of the medication left from the previous prescription (44, 45). If there was a change in dosage or medication—which required a new prescription to be filled before the end of a previous prescription period—the early fill would be considered adherent. CMGR examines the number of days the medication was unavailable for use because of delayed refills in relation to the number of days during a specified time period (44, 45). Kreyenbuhl et al. (35) relied on self-report information from participants and information obtained through the Brief Medication Questionnaire (BMQ) (46), the Beliefs about Medication Questionnaire-Specific Version (BMQ-Specific) (47), the Medication Management Ability Assessment (MMAA) (48), and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (49). This was the only study that provided information that linked medication adherence and glycemic control. Farley et al. (38) and Hansen et al. (39) used Proportion of Days Covered (PDC), which measures the number of days without medication gaps divided by the number of days of observation (50). PDC values range from 0 to 1, with 1 indicating complete adherence. A cutpoint value of  $>.80$  was considered adherent in both Farley et al. (38) and Hansen et al. (39). A summary of the included studies is provided in Table 1.

Overall, improved medication adherence was associated with disease and medical service and medication-related factors. Three studies indicated a positive association between increased number of outpatient clinic visits, antipsychotic medication adherence, and diabetes medication adherence, respectively (34, 37-39). These were the only factors where two separate studies both showed a positive association with medication adherence. Factors that were associated with nonadherence were identified in each of the four categories. Identified factors associated with medication adherence are presented in Table 2.

Kreyenbuhl and colleagues (34) examined Veterans Affairs administrative data for 11,454 participants with schizophrenia and 10,560 participants without schizophrenia over a one-year period. Participants with schizophrenia had an average age of nearly 56 years and were mostly men ( $n=10,906$ ). Medication adherence was measured using MPRs (40-43). Individuals with schizophrenia were more likely to adhere to their oral hypoglycemic medications than individuals without schizophrenia (51% vs. 46%,  $p<.0001$ ). Factors that were

**Table 1** Descriptive Statistics of Included Studies

Author	Sample Size (schizophrenia group only)	Age (M±SD)	Sex	Diagnoses	Setting, Country	Study Type	Medication Type	Measure of Adherence	Adherence	Glycemic Control
Dolder et al. 2003	N=76 (Note: only 24 individuals were taking antidiabetic medication)	54±11 years	72 men; 4 women	41 schizophrenia; 18 schizoaffective disorder; 11 mood disorder with psychotic features; 6 psychosis not otherwise specified	Outpatient clinics, Veterans Affairs San Diego Healthcare System, United States	Retrospective database assessment of computerized medication fill records over 12 months	Antidiabetic medication	Compliant Fill Rate (CFR), Cumulative Mean Gap Ratio (CMGR)	CFR=52% CMGR=15%	Data not available
Farley et al. 2012	N=1,006 (Note: only 280 individuals were taking antidiabetic medication)	N=100 (18–34 years); N=588 (35–54 years); N=318 (55+ years)	334 men; 672 women	1,006 schizophrenia	In- and out-patients, Medstat MarketScan Medicaid files, United States	Retrospective database assessment of medication fill records from 2004 to 2006	Oral antidiabetics medication	Proportion of Days Covered (PDC)	Average PDC for diabetes medication cohort ranged from .65 (maintenance phase of antipsychotic medication treatment) to .86 (acute phase of antipsychotic medication treatment)	Data not available
Hansen et al. 2012	N=33,230 (Note: only 12,349 individuals were taking antidiabetic medication)	48±10 years	14,217 men; 19,013 women	33,230 schizophrenia	In- and out-patients, MarketScan Medicaid files, United States	Retrospective database assessment of medication fill records from 2004 to 2008	Oral antidiabetics medication	Proportion of Days Covered (PDC)	61% had PDC >.80	Data not available
Kreyenbuhl et al. 2010	N=11,454	55.7±10.7 years	10,906 men; 548 women	schizophrenia or schizoaffective disorder	Veterans Affairs National Psychosis Registry, United States	Retrospective database assessment of automated prescription refill records over 12 months	Oral hypoglycemic medications	Medication Possession Ratio (MPR)	Prevalence of adherence (MPR=0.8–1.2) was 51%	Data not available
Kreyenbuhl et al. 2011	N=44	51.1±9.3 years	20 men; 24 women	31 schizophrenia-spectrum disorder; 13 major mood disorder	Out-patient clinics and primary care clinics, United States	Retrospective assessment of medication use over 7 days	Oral or injectable hypoglycemic medications	Medication Adherence Assessment Interview, Brief Medication Questionnaire (BMQ)	73% self-reported adherence to medication	No significant difference between those who reported adherence (7.4±1.8) and nonadherence (7.6±1.8)
Piette et al. 2007	N=1,686	54.9±10.8 years	1,601 men; 85 women	1,686 schizophrenia	Veterans Affairs National Psychosis Registry, United States	Retrospective database assessment of automated prescription refill records over 12 months	Oral hypoglycemic medications	Medication Possession Ratio (MPR)	71% had MPR ≥.80	Data not available

**Table 2** Determinants of Diabetes Medication Adherence in Schizophrenia

Determinant	Positive	Negative	Null
<b>Demographic Factors</b>			
Age			Kreyenbuhl et al. (2010), Kreyenbuhl et al. (2011)
Gender (male)			Dolder et al. (2003)
Homelessness		Kreyenbuhl et al. (2010)	
Married			Kreyenbuhl et al. (2010)
Race (black)		Kreyenbuhl et al. (2010)	
Race (unknown)			Kreyenbuhl et al. (2010)
<b>Psychological and Cognitive Factors</b>			
Beliefs about medication necessity			Kreyenbuhl et al. (2011)
Cognitive impairment			Kreyenbuhl et al. (2011)
Concerns about adverse medication consequences			Kreyenbuhl et al. (2011)
Motivation barriers		Kreyenbuhl et al. (2011)	
Recall barriers		Kreyenbuhl et al. (2011)	
<b>Disease and Medical Service Factors</b>			
Alcohol or substance use disorder		Kreyenbuhl et al. (2010)	
Depression		Kreyenbuhl et al. (2010)	
Prior hospitalizations		Piette et al. (2007)	Kreyenbuhl et al. (2010)
Medical comorbidity		Kreyenbuhl et al. (2010)	
Number of outpatient clinic visits	Kreyenbuhl et al. (2010), Piette et al. (2007)		
Posttraumatic stress disorder			Kreyenbuhl et al. (2010)
<b>Medication Factors</b>			
≤49% of prescription copayment			Kreyenbuhl et al. (2010)
≥50% of prescription copayment	Kreyenbuhl et al. (2010)		
≤50% of prescription refills by mail		Piette et al. (2007)	
>50% of prescription refills by mail	Kreyenbuhl et al. (2010)		
>60 days of medication supply			Kreyenbuhl et al. (2010), Piette et al. (2007)
≤60 days of medication supply		Piette et al. (2007)	
Adherence to antipsychotic medication	Farley et al. (2012), Hansen et al. (2012)		
Filled prescriptions for one medication versus two		Piette et al. (2007)	
Independent medication administration	Kreyenbuhl et al. (2011)		
Medication access barriers		Kreyenbuhl et al. (2011)	
Medication regimen complexity	Kreyenbuhl et al. (2010)		Kreyenbuhl et al. (2011)
Number of drug classes	Piette et al. (2007)		Dolder et al. (2003), Kreyenbuhl et al. (2011)
Prescribed insulin			Kreyenbuhl et al. (2011)

associated with nonadherence to diabetes medication included black race, homelessness, depression, alcohol or substance use disorder, and medical comorbidity. Increased adherence was associated with increased outpatient clinic visits, having prescriptions mailed to the individual, reducing copayments for prescriptions, and increased complexity to medication regimen.

In a study of adherence to hypoglycemic medications and blood glucose control, Kreyenbuhl et al. (35) examined 44 individuals with diabetes and serious mental illness and 30 individuals with diabetes and no diagnosis of serious mental illness. Of the 44 individuals with serious mental illness, 31 were diagnosed with a schizophrenia-spectrum disorder. Participants completed a medication-adherence assessment with research staff, where staff recorded the name, dosage strength, and frequency of administration for all prescribed medications. The Brief Medication Questionnaire (BMQ) (46) was used to assess participants' adherence to medication directions over the past week. Individuals with serious mental illness reported statistically significant higher adherence rates (73%) to hypoglycemic medications than those without serious mental illness (40%) ( $\chi^2=7.9$ ,  $df=1$ ,  $p=.005$ ). For individuals with serious mental illness, blood glucose control levels were not statistically different between those who did ( $7.6\pm 1.8$ ) and did not ( $7.4\pm 1.8$ ) adhere to their medication ( $t=.32$ ,  $p=.75$ ). Researchers suspected that these findings may have been limited by the self-report nature of medication adherence, small sample size, as well as other factors like duration and severity of diabetes, body mass index, levels of physical activity, and diet. Through the BMQ-Specific (47), the MMAA (48), and the RBANS (49) participants self-identified that medication nonadherence was influenced by low motivation, problems remembering to take their medication, and difficulties obtaining their medication. Independent medication administration, versus getting support from family members or professional healthcare workers, was positively correlated with adherence.

In the Dolder et al. (36) study, researchers examined 12 months of medication fill records for 76 participants over the age of 40 years diagnosed with schizophrenia or another psychotic disorder. All participants were Veterans Affairs outpatients and most ( $n=72$ ) were men. Of the 76 participants in the study, only 24 individuals were prescribed oral hypoglycemic medication. The remaining participants were screened for their adherence to oral medication to hypertension ( $n=60$ ) and hyperlipidemia ( $n=28$ ). All participants were taking antipsychotic medication. Medication adherence was calculated through a CFR and CMGR (44, 45). Dolder et al. (36) reported a CFR of 52% and a CMGR of 15% for those participants taking oral hypoglycemic medication. Researchers found no significant differences between medica-

tion types when CFRs ( $F=1.39$ ,  $df=3,184$ ,  $p=.25$ ) and CMGRs ( $F=2.24$ ,  $df=3,184$ ,  $p=.086$ ) were examined. No significant differences existed in adherence rates between genders or for medication quantity.

Piette et al. (37) studied medication adherence among participants diagnosed with schizophrenia, diabetes, and hypertension. Researchers examined one year of data from the Veterans Affairs National Psychosis Registry for 1,686 participants. The majority of participants were men ( $n=1,601$ ) and had an average age of 55 years. Medication adherence was calculated using MPRs for each medication type (40-43). Seventy-one percent of participants were considered adherent to their hypoglycemic medication, and this was significantly greater when compared to their adherence to antipsychotic medication ( $p<.001$ ). Poorer adherence was associated with prior hospitalizations, fewer prescription refills by mail, and regimens with an average of 60 days' supply or less. Adherence was correlated with an increased number of outpatient visits and an increased number of drug classes.

Farley et al. (38) similarly examined the relationship between adherence to antipsychotic medication and cardiometabolic medication in individuals diagnosed with schizophrenia and diabetes, hypertension, and/or hyperlipidemia. A total of 1,006 participants who were newly prescribed antipsychotic treatments were included in a retrospective analysis of Medstat MarketScan Medicaid databases between 2004 and 2006. In total, 672 women were included in the analyses. Individuals were stratified by three age categories: 18-34 years ( $n=100$ ), 35-54 years ( $n=588$ ), and 55+ years ( $n=318$ ). Antipsychotic and cardiometabolic medication adherence was evaluated at three different time periods over the two years of analyses. Time periods pertained to when antipsychotics were initiated and included the initiation period (days 1-90 days), the continuation period (days 91-360), and the maintenance period (days 361-520). Medication adherence was calculated using PDC, with values  $\geq .80$  indicating adherence. Adherence to diabetes medication was highest during the initiation period (mean PDC=.83) and lowest during the maintenance period (mean PDC=.65). Individuals who were adherent to antipsychotic medication were more likely to adhere to their diabetes medication during the continuation (OR=1.72, CI=.94-3.18) and maintenance periods (OR=2.28, CI=1.43-3.67).

Hansen et al. (39) examined antipsychotic and cardiometabolic medication adherence in individuals diagnosed with schizophrenia, diabetes, hypertension, and/or hyperlipidemia. A total of 32,230 individuals were identified in MarketScan Medicaid files between 2004-2008. Participants were mostly women (19,013) and had an average age of  $48\pm 10$  years. All participants were taking antipsychotic medication. A total of 12,349 participants had a diagnosis of diabetes.

Medication adherence was evaluated using PDC. Sixty-one percent of individuals had a PDC  $\geq 80$  and were considered adherent to their diabetes medication. Individuals who were adherent to antipsychotic medication were significantly more likely to be adherent to their diabetes medication (OR=12.7, CI=10.0–14.8).

## Discussion

The purpose of this systematic review was to: 1) evaluate rates of adherence and factors associated with adherence with medication for T2DM in individuals with schizophrenia; and, where possible, 2) examine the relationship between medication adherence and glycemic control. In total, six retrospective studies were included in this review. No prospective studies have been published in this area of study thus far. Three studies examined medication adherence in mostly older men affiliated with Veterans Affairs in the United States (34, 36, 37). Two studies examined medication adherence using Medicaid information (38, 39). In these two studies, more women were included in the analyses than men. With the six studies examined together, more men were included in the analyses than women (27,150 vs. 20,346) and the majority of participants were over the age of 50 years.

Overall, studies confirmed that many individuals with schizophrenia were not adhering to their diabetes medication regimens as adherence rates, for different measurement tools, ranged from 51–85%. Factors that improved adherence included disease and medical service and medication-related factors such as an increased number of outpatient clinic visits, greater percentage of prescription copayment, greater percentage of prescription refills by mail, independent medication administration, medication regimen complexity, adhering to antipsychotic medication, and increased number of prescribed drug classes. Nonadherence to medication was associated with homelessness, race (black), motivation barriers, recall barriers, alcohol or substance use disorder, depression, increased number of prior hospitalizations, medical comorbidity, few prescription refills by mail, fewer than 60 days of medication supply, filled prescriptions for one medication versus two, and general medication access barriers. Given the different sizes of populations examined in these studies, some factors may be considered to have greater external validity than others. For instance, psychological and cognitive and medication-related factors identified by Kreyenbuhl et al. (35) and Dolder et al. (37), where population sizes ranged from 44–72, warrant further study using larger samples to determine their generalizability. Overall, the results of this review identify modifiable factors that can be targeted through interventions to improve adherence to diabetes medication in individuals with schizophrenia.

In comparison to previous reviews that have examined

diabetes medication adherence in the general population, the results of this review are similar. Cramer (21) found that retrospective analyses of adherence to oral hypoglycemic agents ranged 36–93%. Other reviews of the general population have also reported similar findings (51, 52). The results of the current review illustrate that many individuals with schizophrenia and diabetes do not adhere to their diabetes medication and that a complex set of factors influence whether an individual does or does not adhere to their medication. Improved medication adherence is a growing concern for healthcare providers and systems and insurance companies as medication nonadherence has been shown to be associated with increased healthcare costs and utilization, especially those associated with acute care (40, 53, 54). Strategies should be constructed that take into consideration nonmodifiable factors, such as certain demographic factors, but primarily address modifiable factors. In a review of interventions to improve medication adherence in schizophrenia, Zygmunt and colleagues (55) found that programs that addressed multiple factors were more likely to be successful. Of the 39 studies included in their review, behavioral interventions that employed concrete instructions, problem-solving strategies, or motivational techniques were more successful. Zygmunt et al. (55) also stressed that problems with medication adherence are recurring and that booster sessions on an ongoing basis may be needed to continually reinforce adherence. A major recommendation by Zygmunt and colleagues (55) was a need for a theoretical basis to construct interventions to address behaviors related to medication adherence.

There are several important areas where further study is necessary in order to better understand diabetes medication adherence in schizophrenia and how it may be improved. A potential program of research based on the Medical Research Council (MRC) Framework for Complex Interventions may help identify relevant theories and other demographic needs associated with behavior change necessary for increased diabetes medication adherence in schizophrenia. (For a review of the MRC Framework, please see [56].)

This review has identified several modifiable and non-modifiable factors in relation to diabetes medication adherence in schizophrenia; however, the research to date does not show whether these factors are relevant to different subgroups of individuals living with schizophrenia. Currently, no research has thoroughly examined diabetes medication adherence rates or factors related to medication adherence for women, younger individuals, and those who have recently been diagnosed with diabetes. Three of the six studies included in this review examined medication adherence primarily in men (34, 36, 37). In each of these studies, women represented approximately 5% of the study participants who had a diagnosis of schizophrenia. Two studies included large

samples of women; however, no information was presented on whether gender influenced diabetes medication adherence specifically (38, 39). Although Dolder et al. (36) did not show a statistically significant difference between men and women, this conclusion was based on a sample of four women. Each of the studies included in the review also examined diabetes medication adherence mainly in older individuals. Additionally, one study provided information on duration of diabetes where participants had been living with the illness for an average length of nearly 13 years (35), mostly representing individuals who had been living with diabetes for quite some time and presumably accustomed to their condition.

Recent research that has investigated diabetes medication adherence in the general population has shown that women, younger individuals, and those with a recent diagnosis of diabetes to be at greater risk of nonadherence (57). Researchers who conduct future retrospective studies involving individuals with schizophrenia should remain conscious of these limitations in the literature and include larger sample sizes of women, younger individuals under the age of 50 years, and those recently diagnosed with diabetes as these individuals have been shown to be at greater risk of nonadherence. Intervening early and finding opportunities to prevent the onset of complications related to diabetes will produce the greatest health benefits for this population. Future prospective research can help determine what factors are associated with adherence in these populations and help create strategies to accommodate these individuals to improve diabetes medication adherence. As Zygmunt and colleagues (55) have suggested, identified factors can also point researchers to use specific behavioral theories and models to construct interventions that can address psychological and cognitive factors as well as contextual factors associated with disease and medical services and medications.

After examining the existing evidence base, potential interventions aimed at addressing modifiable factors should be evaluated for their feasibility and piloted on a small scale (56). Researchers may wish to conduct small-scale experimental and qualitative studies in order to refine their interventions and better understand how larger, more rigorous research can be conducted. These studies may also help with knowledge translation strategies to broadly disseminate behavior change information in an accessible format. Researchers can further enquire how information is accessed and processed by different identified subgroups as tailored and targeted information has been shown to have a greater impact in changing healthful behaviors (58, 59).

As this review shows, only retrospective research has been conducted in individuals with respect to diabetes medication adherence and schizophrenia. Prospective research

that examines diabetes medication adherence has not been conducted in individuals with schizophrenia. Future research may wish to conduct multi-site, randomized controlled trials given that any research that has examined diabetes medication adherence involving individuals with schizophrenia has been mostly conducted with veterans and only in the United States.

This review has several strengths that should be noted. First, a rigorous methodology was followed to locate and examine studies for inclusion. This was accomplished by adapting the protocols of previous reviews examining diabetes medication adherence in the general population (21, 25). Second, this review is the first to aggregate findings on factors associated with diabetes medication adherence in schizophrenia. This provides information on which factors should be targeted in future interventions and which require further study.

There are a number of limitations with this review that must be mentioned. First, only one of the six studies included in this review presented data on blood glucose levels, which limits any conclusions that can be made about medication adherence and blood glucose control levels. Second, a number of subgroups identified earlier in this discussion were underrepresented in the included studies, which does not allow for a thorough understanding of determinants related to diabetes medication adherence in schizophrenia as a whole. Further research is needed to understand which factors in these subgroups influence medication adherence. Third, population sizes varied greatly, which indicates that some studies carry greater external validity than others. Fourth, the review is limited to studies published in English. Lastly, given the limited number of studies included in this review and the identified differences in sample sizes and adherence measurement tools, a meta-analysis was not produced.

This review illustrates that adherence to diabetes medication in schizophrenia is low and that complex interventions need to be constructed to address both modifiable and nonmodifiable determinants of diabetes medication adherence. Improving diabetes medication adherence is key to improving overall health in individuals with schizophrenia and reducing acute healthcare costs and utilization (38). This review also shows that other behaviors, considered cornerstones in overall diabetes care (60), such as exercise, diet, and blood glucose monitoring, have not been examined in individuals with schizophrenia with respect to medication adherence. Further research is needed to examine diabetes medication adherence in women, younger individuals, and those recently diagnosed with diabetes, as well as to explore behaviors commonly associated with improved medication adherence.



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