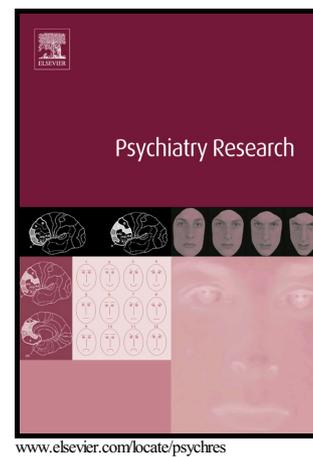


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Running head: Diabetes medication adherence in schizophrenia

Are people with schizophrenia adherent to diabetes medication? A comparative meta-analysis

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Abstract

Individuals living with schizophrenia are 2-3 times more likely to experience type 2 diabetes mellitus. Diabetes medication adherence is essential to reduce morbidity and mortality in this population. We conducted a meta-analysis of diabetes medication adherence among people with schizophrenia, and compared this to those without schizophrenia. A systematic search strategy was used to identify all articles reporting adherence to diabetes medications among patients with schizophrenia. In total, 10 unique studies reporting data from 33,910 people with schizophrenia were included. Random effects meta-analysis showed people with schizophrenia adhered to medication on 77.3% of days prescribed ($n=32080$, 95%CI=73.6%-81%, $I^2=99.2\%$), and adhered on 4.6% more days per year than those without schizophrenia ($p<0.01$, 95%CI=2.4%-6.7%, $I^2=92.5\%$, schizophrenia $n=19367$, controls=170,853). Furthermore, 56% of individuals with schizophrenia ($n=33680$) were considered “adherent” (i.e. >80% adherence over 12-24 month) to diabetes medication, which was significantly more than those without schizophrenia (OR=1.34, 95%CI: 1.18-1.52, $p<0.01$). Factors which were positively associated with diabetes medication adherence were age, number of outpatient visits, along with multiple medication administration variables. Future prospective research should examine diabetes monitoring, medication prescription, and subsequent adherence in fully representative samples. Novel interventions for maximizing compliance to diabetes medication in this vulnerable population should also be explored.

Keywords: schizophrenia, type 2 diabetes mellitus, medication adherence, meta analysis

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1. Introduction

Individuals living with schizophrenia are highly susceptible to type 2 diabetes mellitus (T2DM) (de Hert et al., 2009). Current estimates show that individuals with schizophrenia are 2 to 3 times more likely to acquire T2DM than the general population (Stubbs et al., 2015). It is believed that approximately 10 to 15% of individuals with schizophrenia have T2DM (Vancampfort et al., 2016). A number of factors contribute to a higher T2DM prevalence in this population, including family history, cardio-metabolic side effects of antipsychotic medication, and lifestyle factors such as physical inactivity and poor diet quality (Stubbs et al., 2015).

Higher T2DM prevalence carries a number of health consequences for individuals with schizophrenia. Both T2DM and excess weight are independent risk factors for developing cardiovascular disease and place individuals with schizophrenia at greater risk of early mortality (Ribe et al., 2014). Previous research has demonstrated that as a result of cardiovascular disease, individuals with schizophrenia have a shortened life expectancy of approximately 10 to 20 years (Ribe et al., 2014).

A number of strategies have been recommended for helping individuals with schizophrenia to manage T2DM, and to maintain and promote cardio-metabolic health. These strategies have primarily focused on lifestyle changes, such as increasing physical activity and maintaining a low-calorie and low fat diet (Annamalai and Tek, 2015). Additional strategies have included regular blood glucose monitoring and encouraging adherence to diabetes medication. Medication adherence can be defined as voluntary involvement of taking medication in pursuit of a therapeutic result (Delamater, 2006). Adequate diabetes medication adherence can help individuals to maintain glycemic control and reduce the likelihood of microvascular complications that result from diabetes, including blindness, renal failure, and amputations (Cade, 2008). In the general population, adherence is

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determined by multiple factors including: patient-related (younger age, female gender, smoking, impulsivity ethnic minority groups), condition-related (the presence of depression or other chronic diseases, shorter duration of diabetes, fewer diabetes complications), socioeconomic (lack of financial resources/increased medication costs, lower education level, lack of family support), health system-related (increased distance to nearest pharmacy, lower continuity of care) and therapy-related (concurrent medication use, adverse effects, poor previous experience with medication) (World Health Organization, 2003). In comparison to the general population, individuals with schizophrenia are less likely to receive diabetes education, and less likely to have glycated hemoglobin (HbA1C) and serum lipid levels regularly monitored (Cimo et al., 2012; Dickerson et al., 2005; Goldberg et al. 2007). To our knowledge, only one previous narrative systematic review has examined diabetes medication adherence in people with schizophrenia, and results were limited to only six studies (Gorczynski et al., 2014). The purpose of this study was to provide an update on diabetes medication adherence in individuals with schizophrenia, and apply meta-analytic techniques to obtain an aggregated understanding of diabetes medication adherence rates in people with schizophrenia compared to those without. A secondary purpose of this meta-analysis was to determine factors associated with medication adherence in people with schizophrenia.

2. Methods

This systematic review adhered to the PRISMA statement to ensure transparency and comprehensive reporting of methodology and results (Moher et al., 2009). The protocol for this systematic review adhered directly to the methodology of a previously-published review (Gorczyński et al., 2014), only using an updated search to identify more recent studies. The statistical analyses were also pre-determined in advance of conducting the review to aggregate all eligible data on adherence to anti-diabetic medications in naturalistic settings among people with schizophrenia.

2.1 Search Strategy and Selection Criteria

All studies included in an earlier systematic review of anti-diabetes medication adherence in schizophrenia (Gorczyński et al., 2014) were automatically eligible for this meta-analysis. We also performed an updated electronic database search of Cochrane Central Register of Controlled Trials, AMED (Allied and Complementary Medicine), Embase, MEDLINE, PsycINFO, PsycARTICLES and Ovid MEDLINE using the following keyword search terms: “compliance” or “adherence” AND “hypoglycemic agents” or “insulin” or “metformin” or “diabetes” AND “psychosis” or “antipsychotic” or “schiz*”. This search was conducted from 01/01/2013 – 08/02/2016 in order to update the results of the earlier systematic review which used an identical search protocol. The reference lists of retrieved articles were searched and a basic search of Google Scholar was conducted using the same key words in an effort to identify additional relevant publications.

Only peer-reviewed, English-language, original research articles were included in this review. We aimed to include all studies which reported adherence to diabetes medications among patients with schizophrenia in naturalistic settings as a dependent variable. Our review focused on T2DM. Intervention studies reporting adherence rates over the course of a

randomized trial were not eligible for inclusion, since medication adherence in clinical trials differs significantly from real-life observations.

Studies were excluded from this review if they failed to report adherence data for diabetes medication in schizophrenia or schizophrenia-like disorders. Studies with mixed samples of psychiatric disorders were eligible if >80% of the sample had a diagnosis of schizophrenia/schizoaffective disorder. Data from studies in which <80% of the sample had a confirmed diagnosis of schizophrenia / schizophrenia-like disorders were only included if adherence specifically among the patients with schizophrenia / schizophrenia-like disorders could be accurately determined and extracted. Where this was not reported, the corresponding author of the article was contacted to obtain this information. Studies which did not disclose specific diagnoses of the sample were eligible for inclusion provided that the entire sample was receiving antipsychotic medications.

2.2 Data Extraction and Analysis

Two reviewers (JF and PG) screened the articles independently to assess eligibility. Any discrepancies were resolved through discussion between authors until agreement was reached. A systematic tool was developed to extract the following information from each study:

- (1) Study characteristics: sample size, demographics, location and setting, study design, type of medications examined, and measurement methods used.
- (2) Adherence to diabetes medications: (i) mean daily adherence i.e. number of days-per-year on which medication was taken as prescribed, and (ii) the number of patients who were 'adherent', defined as achieving >80% adherence to medication regimes (Kreyenbuhl et al., 2010). Identical data was also extracted from non-schizophrenia control samples.

Additionally, any factors found to be associated with diabetes medication adherence in patients with schizophrenia were extracted and systematically reviewed.

2.3 Statistical Analyses

Statistical analysis was conducted in OpenMetaAnalyst (Wallace et al., 2009). Random-effects models were applied to all meta-analyses in order to account for the variance between studies (DerSimonian and Laird, 1986).

The primary outcome was the overall daily adherence to diabetes medication regimes in people with schizophrenia, as assessed by quantitative measures. Data from all studies reporting the number of days-per-year on which medication was taken as prescribed were pooled (Wallace et al., 2009), to determine overall adherence. Following this, pooled estimates of daily adherence rates in schizophrenia and non-schizophrenia samples were compared to estimate the difference in adherence between the two groups.

As a secondary outcome, we examined the proportion of schizophrenia patients who were 'adherent' to diabetes medications (i.e. >80% on objective measures (Kreyenbuhl et al., 2010)). Therefore, the proportions of adherent patients were pooled across all studies reporting this variable, in order to calculate a weighted estimate with 95% confidence intervals. Additionally, the numbers of adherent people with schizophrenia was compared to samples without schizophrenia using odds-ratio meta-analysis.

Variance between studies was assessed using Cochran's Q and reported as I^2 , which quantifies the degree of variance resulting from between-study heterogeneity, rather than by chance. The degree of potential publication bias was examined through visual inspection of funnel-plots of the association between proportion estimate and SE standard errors and Egger's test for small-study bias. Eligible studies reporting data not able to be pooled for meta-analysis were included in the systematic review of study findings.

To assess determinants of diabetes medication adherence, a framework established by Gorczynski et al. (2014) was used for this analysis. Independent variables that were shown to be significantly associated with diabetes medication adherence (dependent variable) were reported to have a statistically positive or negative association. Factors found to have no significant association with diabetes medication adherence were reported as null. Factors of diabetes medication adherence were separated into the following categories: demographic, psychological and cognitive, disease and medical service, and medication.

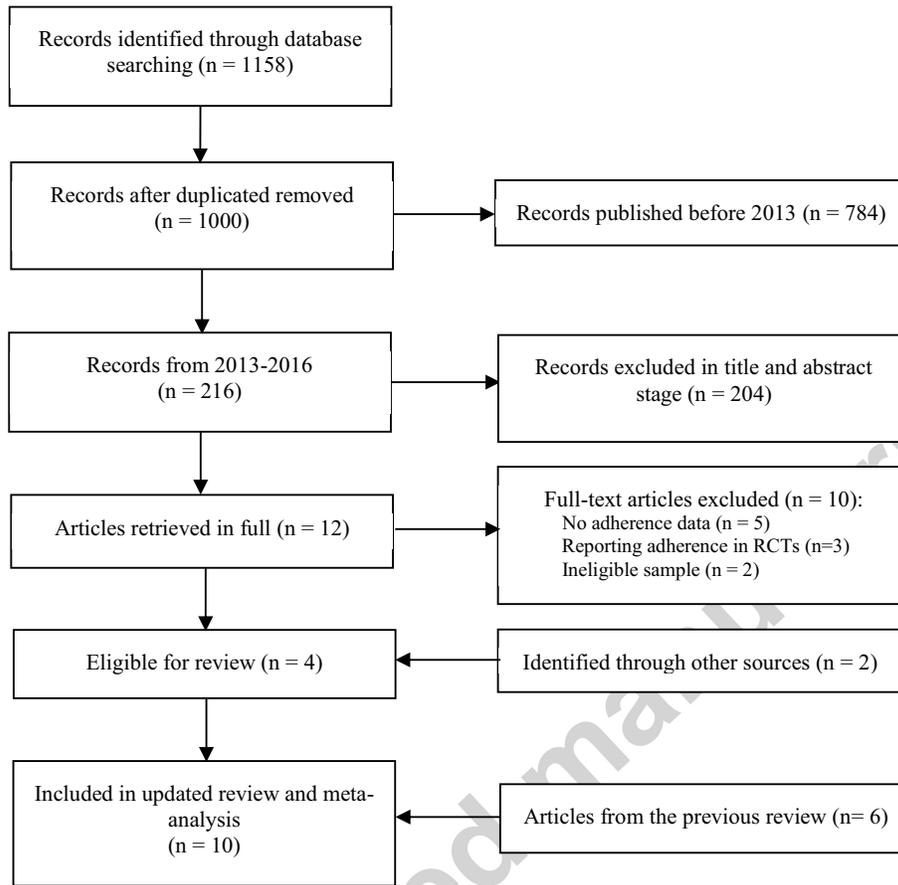
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3. Results

3.1 Search results

The PRISMA search process is presented in Figure 1. The initial database search returned 1158 articles, which was reduced to 1000 after duplicates were removed. Of the 216 articles published since 01/01/2013 (i.e. our previous search Gorczynski *et al.*(2014)), 204 were found to be ineligible by title and abstract screening. The 12 remaining articles were retrieved in full and screened for eligibility. Of those, 2 met eligibility criteria (Desai *et al.*, 2014; Simard *et al.*, 2015). Additionally, searching the reference lists of retrieved studies identified 2 further studies which were eligible for inclusion in this review (Dixon *et al.*, 2004; Nelson *et al.*, 2011). Therefore, these 4 articles were added to the 6 studies from our original search (Dolder *et al.*, 2003; Farley *et al.*, 2012; Hansen *et al.*, 2012; Kreyenbuhl *et al.*, 2011; Kreyenbuhl *et al.*, 2010;).

Figure 1. PRISMA study selection process



In total, 10 articles were included in this review, reporting data from 33,910 psychiatric patients, 94.6% of which had a confirmed diagnosis of schizophrenia / schizoaffective disorder. 90.4% were male and the mean age was 53.8 years (median=54, range=46-67). Studies' characteristics are detailed in Table 1. Eight studies were conducted through retrospective analysis of medication fill records to provide objective measures of compliance. Two studies were conducted through self-report survey measures of adherence. All studies were conducted in USA (n=9) or Canada (n=1). Additional data necessary for meta-analyses was obtained from corresponding authors of 4 eligible studies (of 6 authors contacted) (Desai et al., 2014; Farley et al., 2012; Kreyenbuhl et al., 2010; Simard et al., 2015). Funnel plots were generated for each analysis, and visual inspection of these provided no indication of publication bias

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Table 1. Characteristics of included studies.

Author (Date)	SZ Sample (% male)	Mean age (SD)	Diagnostic information	Setting	Study Type	Medication type	Measure	Adherence
Dixon et al. 2004	100 (58% male)	48.1 ±9.1	100% SZ	Outpatients recruited in Baltimore, USA.	Self-reported medication use over last 7 days.	Hypoglycaemic medications (>76% OADs)	Diabetes Self-Care Activities (SDSCA)	Mean score of 94.4±17.3 for the last week.
Simard et al. 2015	6030 (49% male)	67 ±10	100% SZ	RAMQ Database, 2000- 2009. Quebec, Canada	Retrospective database analysis over 2 years	Various OADs	Medication Possession Ratio (MPR)	81.3% (±27.8) overall daily adherence in SZ sample. 72% of people with SZ were adherent (MPR ≥80%).
Hansen et al. 2012	12349 (42.8% male)	48 ±10	100% SZ	National Medicaid database, 2004-2008, USA.	Retrospective database analysis over 4 years	Unspecified OADs	Proportion of Davys covered (PDC)	80.3% (±22.3) overall daily adherence in SZ sample. 60.6% of people with SZ were adherent (PDC ≥80%).
Desai et al. 2014	1821 (37.7% male)	46 ±11.9	100% Antipsychotic users	Texas Medicaid database, 2008-2011. USA	Retrospective database analysis over 1 year	Unspecified OADs	Proportion of Davys covered (PDC)	63% (±29) overall daily adherence in SZ sample. 37.2% of people with SZ were adherent (PDC ≥80%).
Nelson et al. 2011	62 (96.8% male)	57.9 ±7	68% SZ, 29% SZ-AF, 3% NOS	Kansas City Veterans Affairs Medical Center database, 2008. USA	Retrospective database analysis over 1 year	54.8% Metformin 37.1% Sulfonylurea 8 Thiazolidinedione	Cumulative mean gap ratio (CMGR)	15.8% (±29) of days were not covered by medications in SZ sample.
Farley et al. 2012	340 (33.2% male)	NS	100% SZ	Medstat MarketScan database, 2004-2008. USA.	Retrospective database analysis over 2 years	Unspecified OADs	Proportion of Davys covered (PDC)	Daily adherence in people with SZ ranged from 86% in first year of OAD treatment, to 65% in later years.
Dolder et al. 2003	24 (94.7% male)	54 ±11	78% SZ / SZ-AF 14% MD psychotic features, 8% P-NOS	Veterans Affairs San Diego Healthcare System. USA	Retrospective database analysis over 1 year	OADs. Mostly sulfonylureas (58%, N =14)	Cumulative mean gap ratio (CMGR). Compliant fill rate (CFR).	15% (±17) of days were not covered by medications in SZ sample. 52% of prescription fills were obtained on time (CFR).
Kreyenbuhl et al. 2011	44 (45.5% male)	51.1	70% SZ, 30% MD with psychotic features	Outpatients recruited in Baltimore, USA	Self-reported medication use over last 7 days	Any hypoglycaemic medications	BMQ – Brief medication questionnaire.	73% of people with SZ were 'adherent' over previous week.
Kreyenbuhl et al. 2010	11454 (95.2% male)	55.7 ±10.7	All SZ or SZ-AF	Veterans Affairs National Psychosis Registry, 2001- 2003. USA.	Retrospective database analysis over 1 year.	Unspecified OADs	Medication Possession Ratio (MPR)	80.9% (±29) overall daily adherence in SZ sample. 51% of people with SZ were adherent (MPR ≥80%).

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Piette et al. 2007	1686 (95% male)	54.9 ±10.8	100% SZ	Veterans Affairs National Psychosis Registry, 2000- 2001, USA	Retrospective database analysis over 1 year.	Unspecified OADs	Medication Possession Ratio (MPR)	71% of people with SZ were adherent (MPR ≥80%)
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MD, mood disorder; OAD, oral antidiabetics; P-NOS, psychosis not otherwise specified; SZ, schizophrenia; SZ-AF, schizoaffective disorder

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3.2 Daily adherence rates

Seven studies reported days-per-year adherence across 32,080 patients with schizophrenia (Desai et al., 2014; Dolder et al., 2003; Farley et al., 2012; Hansen et al., 2012; Kreyenbuhl et al., 2010; Nelson et al., 2011; Simard et al., 2015). These were calculated from prescription fill rates, using medication possession ratios (MPRs), Percentage of Days Covered (PDCs), or Cumulative Mean Gap Ratios (CMGRs) over a 1-2 year period (see Table 1). A random-effects meta-analysis found that people with schizophrenia adhered to medication on 77.3% of the days (95% CI=73.6% to 81%, $Q=722$, $p<0.01$, $I^2=99.2\%$) (Figure 2).

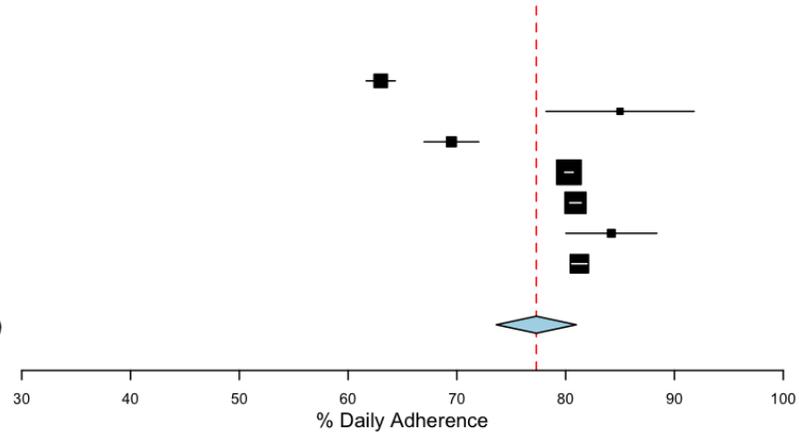
Among these studies, 4 compared daily adherence in 19,367 people with schizophrenia to 170,853 people without schizophrenia (Desai et al., 2014; Kreyenbuhl et al., 2010; Nelson et al., 2011; Simard et al., 2015). Daily adherence in the non-schizophrenia samples was 72.5% (95% CI=66.4% to 78.6%, $Q=1365$, $I^2=99.78$). A comparative meta-analysis found that those with schizophrenia had a 4.6% higher daily adherence rates than people without schizophrenia ($p<0.01$, 95%CI=2.4%-6.7%, $Q=40$, $p<0.01$, $I^2=92.5\%$), equating to approximately 17 more days per-year adherent to medication.

Figure 2. Percentage overall adherence (by fill rates)

Studies

Desai et al. 2014
Dolder et al. 2003
Farley et al. 2012
Hansen et al. 2012
Kreyenbuhl et al. 2010
Nelson et al. 2011
Simard et al. 2015

Overall ($I^2=9917\%$, $P<0.001$)



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3.3 Proportion of adherent patients

Six studies used prescription fill records from 33,680 patients with schizophrenia to determine the proportion who were ‘adherent’ (i.e. with at least 80% of days covered by medications) over a 12-month or 24-month timeframe (Desai et al., 2014; Farley et al., 2012; Hansen et al., 2012; Kreyenbuhl et al., 2010; Kreyenbuhl et al., 2011; Nelson et al., 2011; Piette et al., 2007; Simard et al., 2015). In total, 57.6% of patients with schizophrenia were adherent to diabetes medications (N=6, n=33,680; 95% CI=48.5%-66.5%, Q=1243, $p<0.01$, $I^2=99.6\%$). Three of these studies compared the numbers of people reaching 80% adherence in samples with schizophrenia against samples without schizophrenia (Desai et al., 2014; Kreyenbuhl et al., 2010; Simard et al., 2015). In the non-schizophrenia samples, 46.3% of people were classified adherent to anti-diabetic medications (n=170,791, 95% CI=25.7% to 67.0%, Q=3249.8, $I^2=99.93$). A comparative odd-ratio meta-analysis found that people with schizophrenia (n=19,305) were significantly more likely than people without schizophrenia and diabetes (n=170,791) to be adherent to diabetes medication (OR=1.34, 95% CI=1.18-1.52, $p<0.01$).

This difference was also consistently observed within the studies, as all 3 independently observed that people with schizophrenia were significantly more likely to achieve >80% adherence than their control samples (Desai et al., 2014; Kreyenbuhl et al., 2010; Simard et al., 2015). One further study using self-report measures (and thus not included in the meta-analysis) (Kreyenbuhl et al., 2011) also found that people with schizophrenia were more likely to be adherent over the previous week than people without mental illness.

3.4 Determinants of diabetes medication adherence

Overall, diabetes medication adherence was positively associated with younger age, a higher number of outpatient visits, higher copayments, larger portions of prescriptions

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filled, and independent medication administration. Factors that negatively affected medication adherence included race (black), homelessness, low motivation, difficulties with memory, medical co-morbidity, smaller portions of filled prescriptions, and fewer days of medication being issued. Mixed results were found for prior hospitalizations, adherence to antipsychotic medication, medication regimen complexity, and increased number of drug classes. Full results can be found in Table 2.

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Table 2. Correlates of diabetes medication adherence in schizophrenia

Determinant	Positive association	Negative association	Null
Demographic Factors			
Age	Desai. 2014 (N=1821) Kreyenbuhl. 2010 (N=11454) Kreyenbuhl. 2011 (N=44)		
Gender (male)			Desai. 2014 (N=1821) Dolder. 2003 (N=24)
Homelessness		Kreyenbuhl. 2010 (N=11454)	
Married			Kreyenbuhl. 2010 (N=11454)
Race (black)		Kreyenbuhl. 2010 (N=11454)	
Race (unknown)			Kreyenbuhl. 2010 (N=11454)
Psychological and Cognitive Factors			
Beliefs about medication necessity			Kreyenbuhl. 2011 (N=44)
Concerns about adverse effects			Kreyenbuhl. 2011 (N=44)
Cognitive impairment			Kreyenbuhl. 2011 (N=44)
Motivation barriers		Kreyenbuhl. 2011 (N=44)	
Recall barriers		Kreyenbuhl. 2011 (N=44)	
Disease and Medical Service Factors			
Alcohol / Substance use disorder		Kreyenbuhl. 2010 (N=11454)	
Depression		Kreyenbuhl. 2011 (N=44)	

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Prior hospitalisations		Piette. 2007 (N=1686)	Kreyenbuhl. 2010 (N=11454)
Medical comorbidity		Kreyenbuhl. 2010 (N=11454)	
Number of outpatient clinic visits	Kreyenbuhl. 2010 (N=11454) Piette. 2007 (N=1686)		
PTSD			Kreyenbuhl. 2010 (N=11454)
Medication Factors			
<50% prescription copayment			Kreyenbuhl. 2010 (N=11454)
>50% of prescription copayment	Kreyenbuhl. 2010 (N=11454)		
<50% of prescription		Piette. 2007 (N=1686)	
>50% of prescription	Kreyenbuhl. 2010 (N=11454)		
> 60 days of medication			Kreyenbuhl. 2010 (N=11454) Piette. 2007 (N=1686)
< 60 days of medication		Desai. 2014 (N=1821) Piette.(2007)	
Adherence to antipsychotics	Hansen. 2014 (N=12349) Nelson. 2011 (N=62) Farley. 2012 (N=340)		Kreyenbuhl. 2011 (N=44)
Filled prescriptions for one med vs. two		Piette. 2007 (N=1686)	
Independent medication administration	Kreyenbuhl. 2011 (N=44)		
Medication access barriers		Kreyenbuhl. 2011 (N=44)	
Medication regimen complexity	Kreyenbuhl. 2010 (N=11454)		Kreyenbuhl. 2011 (N=44)
Number of drug classes	Piette. 2007 (N=1686)		Dolder. 2003 (N=24) Kreyenbuhl. 2011

Prescribed insulin	(N=44) Kreyenbuhl. 2011 (N=44)
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4. Discussion

The purpose of this systematic review was to provide the first meta-analysis investigating diabetes medication adherence in individuals with schizophrenia and compare this with the general population. Results showed that, overall, people with schizophrenia were adherent to their diabetes medication on 77.3% of days. People with schizophrenia also adhered to medication on 17 more days per-year than controls without schizophrenia. For studies that examined proportions of patients who were ‘adherent’ (i.e. >80% compliance over a 12- or 24-month period), 57.6% of individuals with schizophrenia were deemed adherent. Furthermore, they were 1.34 times more likely to be adherent to diabetes medication when compared to individuals without schizophrenia.

The results of this meta-analysis build upon existing knowledge about diabetes medication adherence in people with schizophrenia (Gorczynski et al., 2014). Although examining fewer studies and without meta-analytic techniques, this previous review found that adherence rates were between 51-85%, (as assessed by objective measures). Factors that were positively associated with diabetes medication adherence were increased number of outpatient clinic visits, $\geq 50\%$ prescription copayments, > 50 prescription refills by mail, adherence to antipsychotic medication, and independent medication administration.

Previous evidence shows that the physical health of people with schizophrenia is often neglected, and they are less likely to receive appropriate medications for cardiometabolic disorders (Mitchell et al., 2012). Despite this, the results from this meta-analysis are encouraging, showing that those who do receive diabetes treatment adhere better than the general population. This challenges the ‘therapeutic nihilism’ which often remains towards physical health care of people with schizophrenia, and reinforces the value of routine cardiometabolic screening and interventions in mental health services (Lambert and Newcomer, 2009).

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However, it should be acknowledged that diabetes medication adherence rates in the general population and those living with schizophrenia are very similar overall, with many shared factors affecting medication adherence, including having experience being adherent to other forms of medication and being older. For instance, a recent meta-analysis conducted by Iglay *et al.* (2015) found that daily diabetes medication adherence (MPR) was 75.3% in the general population (Iglay *et al.*, 2015); which is only slightly less than the 77.3% adherence we observed in the schizophrenia population. This is also the case when comparing these findings to other reviews of diabetes medication adherence in the general population. Cramer and colleagues found daily medication adherence to be 58% over the previous 12 months (Cramer *et al.*, 2008), and Odegard and Capoccia (2007) found mean medication adherence rates between 31 and 87%.

Results also showed that a significant proportion of people with schizophrenia remain non-adherent to diabetes medications. Understanding factors that influence medication adherence could improve overall care, and guide healthcare professionals to increase the likelihood of treatment success (Curkendall *et al.*, 2013). Factors shown to influence diabetes medication adherence in the general population include patient's understanding of the importance and benefits of treatment, perceived regime complexity, and emotional well-being (Rubin, 2005) – all of which could feasibly be even greater issues for people with schizophrenia. Further exploring the behavioural and environmental determinants associated with diabetes medication adherence in schizophrenia would inform the creation of rigorous interventions (e.g. providing patients with detailed instructions and concrete problem-solving strategies such as reminders, self-monitoring tools, cues, reinforcements) (El-mallakh and Findlay *et al.*, 2015). For instance, a review by El-Mallakh and Findlay (2015) points to various family and clinician support services that are available to help patients with schizophrenia better adhere to their medication (Zygmunt *et al.*, 2002). These services include multi-cultural education workshops, mobile- and computer-based technologies, reminder

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phone calls, motivational interviewing, cognitive behavioural therapy, as well as home visits. However, medication adherence rates following such interventions vary, with not all interventions showing long-term success (Zygmunt et al., 2002). Additionally, all intervention trials pertained to anti-psychotic medication rather than diabetes medication. Since the physical healthcare of people with schizophrenia is often neglected, theory-driven interventions that take into account determinants known to be associated specifically with diabetes medication adherence in this population are urgently needed.

Although this review provides the first meta-analytic summary of diabetes medication adherence in schizophrenia, several limitations should be noted. First, every effort was made to contact study authors by email for additional study details, however some authors did not respond, thus excluding some study data from the meta-analyses, and leaving insufficient data for meta-regression analysis of variables which might predict medication adherence (age, gender, etc.). However, regardless of data eligibility, all relevant studies examining diabetes medication adherence were systematically reviewed, along with any reported factors associated with adherence, to provide a more thorough overall understanding of diabetes medication adherence.

Second, many studies relied on medication possession ratios (MPR) as proxies for medication adherence, which does not fully confirm whether participants actually ingested their medication. Despite this limitation, MPR is still widely used as an indirect measure for medication adherence (Kreyenbuhl et al., 2010), and by comparing MPRs across schizophrenia and other samples, meaningful conclusions can be obtained (Kreyenbuhl et al., 2010). Furthermore, a strength of this review is that all meta-analytic findings were based on objective measurements (e.g. medication possession and prescription fill rates), as only two studies used subjective (self-report) measures of adherence; one for daily adherence (Dixon et al. 2004), one for number of adherent patients (Kreyenbuhl et al. 2011) - and thus were not suitable for inclusion in meta-analyses.

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A third limitation is that several of the included studies examined diabetes medication adherence only in older men who are affiliated with Veterans Affairs living in the USA. Such sampling limits the generalizability of our findings to younger individuals, women, and those with or without access to other healthcare systems. Caution should be taken when interpreting our results given these sampling compositions.

A final limitation is the statistical heterogeneity found in all of the meta-analyses conducted on adherence data (as indicated by significant Cochran's Q values and high I^2 values). This degree of statistical heterogeneity is perhaps surprising, given that most of the included studies used similar samples, measures, locations and time-frames to examine medication adherence. Although the between-study heterogeneity was accounted for by the random-effects models used when computing our proportional estimates, further investigation is required to determine which underlying factors may drive the differences in adherence to diabetes medications across different samples of people with schizophrenia. Furthermore, despite the statistical heterogeneity identified in our analyses, the reasonably narrow 95% confidence intervals (i.e. 73.6% - 83% daily adherence rates found among people with schizophrenia; 2.4 - 6.7% higher than general population) is a strength of the findings, as is the consistency of findings at study-level. For instance, all 3 studies which compared numbers of 'adherent' patients in schizophrenia vs. non-schizophrenia samples found that people with schizophrenia were significantly more likely to be adherent than control samples (Desai et al., 2014; Kreyenbuhl et al., 2010; Simard et al., 2015)).

It should also be considered that people with schizophrenia are significantly less likely to be prescribed appropriate medications for their physical health conditions (Piette et al., 2007). Therefore, the schizophrenia samples used in these analyses may mostly represent those patients with more severe diabetes symptoms, or longer course of illness. There was insufficient data reported by the studies to examine diabetes illness duration, and no information on the frequency of diabetes monitoring for the samples studies. Additionally, all

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of the studies used retrospective methods to assess adherence. Future research should utilize prospective designs, while also measuring the frequency of physical health assessments and medications prescriptions in people with schizophrenia. Specifically, researching these aspects of physical health care among people in the early stages of psychosis (or recently initiating antipsychotic treatment) would provide novel insights into uptake and adherence of diabetes medications in schizophrenia.

In conclusion, our results suggest that diabetes medication adherence in individuals with schizophrenia is higher than those in the general population. Other meta-analyses examining diabetes medication adherence in those without schizophrenia support these findings. However, diabetes medication adherence for individuals with schizophrenia is still insufficient, and theory based strategies are needed to address this in order to improve physical health outcomes, given the current inequalities experienced by this patient group. Left untreated, diabetes medication non-adherence can have profound consequences on patient morbidity and mortality. Thus, prospective research is now needed to examine the efficaciousness and effectiveness of diabetes medication adherence interventions.

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Highlights

- Individuals living with schizophrenia are highly susceptible to type 2 diabetes mellitus
- Diabetes medication adherence is essential to reduce morbidity and mortality
- Individuals with schizophrenia are less likely to receive diabetes education, and less likely to have glycated hemoglobin (HbA1C) and serum lipid levels regularly monitored
- individuals with schizophrenia are more adherent to diabetes medication than those without schizophrenia
- Diabetes medication adherence in individuals with schizophrenia is influenced by age, number of outpatient visits