Exploring the Relationship Between Depression and Adherence in Individuals with Type 2 Diabetes

by

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ABSTRACT

Background: Depression is a well-known risk factor for poor medication adherence in individuals with diabetes; however, this association is based on cross-sectional and cohort studies measuring adherence after depression is diagnosed. Symptoms of depression often progress before medical attention is sought and diagnosis is made by a clinician. Prodromal symptoms of depression could affect medication adherence earlier than currently reported in literature. Additionally, little is known about changes in adherence rates once depression is treated. Given the strong association between depression and poor adherence to antihyperglycemic medications, early recognition and treatment of depression may improve adherence, leading to better glycemic control and prevention of future complications.

Objectives: In individuals with diabetes and a new episode of depression, I sought to: 1) determine if symptoms of depression occurring before a diagnosis are associated with poor medication adherence; 2) determine if treatment of depression affects adherence to oral antihyperglycemic medications.

Methods: Two retrospective cohort studies following adult new metformin users identified in Alberta Health's administrative database between 2008 and 2018. Both studies identified a new depressive episode ≥1 year after metformin initiation using a validated case definition for depression. The first study examined adherence patterns in the year before the depression date. People with a new depressive episode were the exposed group and those without depression served as controls. Proportion of Days Covered (PDC) and Group Based Trajectory Modelling (GBTM)

were used to examine adherence to oral antihyperglycemic medications one year prior to the depression date. Multivariable logistic regression was used to determine if depression was independently associated with a higher risk of poor adherence antecedent to depression diagnosis. The second study examined association between treatment of a new depressive episode and adherence. The exposure group included those who received at least 2 dispensations of any antidepressant medication within 90 days of depression date while the control group included those with <2 dispensations for any antidepressant medication. PDC was used to calculate adherence to oral antihyperglycemics on days 91-270 from the depression date. Multivariable logistic regression was used to determine if pharmacologic treatment of depression was associated with a lower risk of poor adherence to oral antihyperglycemic medications.

Results: 165,056 (77%) new metformin users were identified from 214,762 individuals dispensed an oral antihyperglycemic. A total of 31,513 (19.1%) new metformin users had at least 1 depression-related service record after initiating metformin. Of those, 17,385 (10.5%) had their first depression-related service record at least one year after starting metformin. The mean duration between metformin initiation and a new episode of depression was 3.0 (SD 1.6) years.

In the first study, individuals with depression were more likely to have poor adherence to oral antihyperglycemic medications (PDC <0.80) compared to controls (adjusted odds ratio 1.21; 95% CI 1.17, 1.26). Five trajectories were identified: nearly perfect adherence (PDC >0.95 [34.8% of cohort]), discontinued antihyperglycemics (PDC=0 [18.3% of cohort], poor initial adherence (PDC 0.75) that declined either rapidly (9.2% of cohort) or

gradually (30.1% of cohort), and poor initial adherence (PDC 0.26) that increased gradually (7.6% of cohort). Individuals with depression were more likely to be in one of the four trajectories of poor adherence compared to controls (adjusted odds ratio 1.24; 95% CI 1.19-1.29).

The second study included 7,220 (22.9%) individuals with a new depressive episode who had at least 1 year of data available before their study exit date, no antidepressant dispensations in the previous 6 months and not hospitalized for >50% of the outcome assessment window. A total 1,899 (26.3%) received ≥2 dispensations for antidepressants within 90 days of index date. After adjusting for other comorbidities and characteristics at baseline, individuals treated for depression were associated with a lower, but non-significant likelihood of poor adherence compared to those with no antidepressant treatment (adjusted odds ratio 0.91; 95%CI 0.81,1.02).

Conclusion: Individuals with a depressive episode were more likely to have poor adherence in the year preceding diagnosis. Although treatment of a new depressive episode appears to be associated with a lower likelihood of poor adherence, the observed association did not reach statistical significance. These studies suggest depression screening and treatment may improve care for patients living with type 2 diabetes. By following adherence patterns, clinicians may identify individuals with diabetes who are experiencing symptoms of depression earlier and intervene sooner.

PREFACE

This thesis is an original work by Diva Niaz. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Pro00066037.

The studies in this thesis are based in part on data provided by Alberta Health. The interpretation and conclusions contained herein are those of the researchers and do not necessarily represent the views of the Government of Alberta. Neither the Government of Alberta nor Alberta Health express any opinion in relation to this study.

A version of Chapter 2 has been submitted for peer review: "*Niaz D, Necyk C, Simpson S.H., Depression and Antecedent Medication Adherence in a Cohort of New Metformin Users.*"

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LIST OF ABBREVIATIONS

CANMAT: Canadian Network for Mood and Anxiety Treatments

CI: Confidence Interval

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders 4th Edition

GBTM: Group Based Trajectory Modelling

HbA1c: Hemoglobin A1c

ICD: International Classification of Diseases

IDF: International Diabetes Federation

MPR: Medication Possession Ratio

PDC: Proportion of Days Covered

OAH: Oral Antihyperglycemic Medications

OR: Odds Ratio

SD: Standard Deviation

VIF: Variance Inflation Factor

WHO: World Health Organization

CHAPTER 1: Overview

1.1 Introduction

1.1.1 Type 2 Diabetes

Globally, the prevalence of diabetes mellitus has reached epidemic status. In 2019, 463 million adults were living with diabetes and the International Diabetes Federation (IDF) projects this will soar to 700 million by 2045.(1) The IDF also reports one in five individuals who are 65 years of age or older have diabetes and one in three Canadians is living with diabetes.(1) Type 2 diabetes accounts for 90% of people living with diabetes.(2) Type 2 diabetes is a progressive disease that leads to chronic hyperglycemia due to inability of the human body to produce and secrete insulin or effectively use insulin.(3) As type 2 diabetes is a progressive chronic disease, individuals need to maintain a balanced diet, continue to be physically active, diligently monitor blood glucose levels, and manage complex medication regimens.(4, 5) Collectively, these ongoing self-care activities place a significant burden on individuals and their families. The number of individuals living with diabetes continues to grow at a staggering rate and the importance of addressing contributing factors to suboptimal self-care activities, including medication adherence, need to be highlighted.(6)

Management of type 2 diabetes requires a multifaceted and long-term approach of integrating both lifestyle interventions and pharmacological treatments. Lifestyle interventions promote a healthy lifestyle through diet and exercise. In individuals with type 2 diabetes, progression of the disease worsens glucose control over time and lifestyle interventions are no longer sufficient to achieve and maintain blood glucose control. Treatment with antihyperglycemic medications in addition to lifestyle interventions becomes crucial. Using antihyperglycemic medications has shown benefits in safely and effectively reducing blood

glucose to avoid risk of diabetes related complications.(7, 8) In Canada, clinical practice guidelines recommend timely initiation of metformin as the first-line oral antihyperglycemic medication to manage type 2 diabetes (9) to reduce the risk of microvascular (e.g., retinopathy, nephropathy, neuropathy) and macrovascular (e.g., heart disease, stroke, end-stage renal disease) complications.(10) Subsequent treatment intensification with other antihyperglycemic medications are often required when an individual's blood glucose is no longer controlled. These additions contribute to the complexity of treatment in type 2 diabetes as a response to the progressive nature of this disease. Although individuals may begin with metformin monotherapy, a majority of individuals will be on two or more antihyperglycemic medications or insulin as hyperglycemia intensifies with duration of diabetes.(11, 12)

1.1.2 Depression

Depression is another chronic disease with a high prevalence worldwide and, according to the World Health Organization, more than 264 million people of all ages suffer from depression globally.(13) It is a well-known risk factor for poor self-management of many chronic conditions, including diabetes.(14-17) Depression is often characterized by low mood or a loss of interest in usual activities that can negatively affect an individual's thoughts, feelings and behavior. The Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV) characterizes depression as having either or both aforementioned core symptoms with at least five associated symptoms of sleep disturbance, loss of appetite, restlessness, decreased energy, feelings of worthlessness and guilt or suicidal ideation.(18) Given that depression is a chronic illness with frequent recurrent episodes, interventions need to be tailored to each individual to avoid distress, social and occupational functional impairment.(19)

Treatment of depression consists of interventions that are non-pharmacological, pharmacological or both.(20) Although effective treatments are available as outlined by the Canadian Network of Mood and Anxiety Treatments (CANMAT), many individuals often delay or do not seek treatment.(21) First line treatment for individuals with depression range from psychoeducation, psychological counselling, to pharmacological therapy with antidepressants.(20) Adherence to these interventions is important to achieve and maintain remission from an active episode of depression.(22)

1.1.3 Medication Adherence Using Administrative Data

Adherence refers to how a medication is taken based on an agreement between an individual and clinician. Measures of adherence may include individuals' self-reports, surveys, pill counts, electronic monitoring systems, pharmacy records, or administrative databases.(23) There is no gold standard measure for adherence(17, 24); however, dispensation records in administrative databases are more commonly used in epidemiological studies. Administrative databases provide objective information for billing purposes, and are a convenient, feasible, non-invasive way to measure adherence. A major limitation of using administrative databases is the assumption that medication claims are perfectly aligned with medication consumption. When individuals do not use all of the pills they obtain, using this source of data will overestimate adherence. Regardless, the use of administrative data is highly correlated with other measures of adherence(25), and can be used to provide adherence information with both validity and integrity.(25, 26)

1.1.4 Traditional Measure of Adherence: Proportion of Days Covered

Using administrative data, adherence is commonly measured by calculating a medication possession ratio (MPR) or proportion of days covered (PDC).(23) An MPR is calculated as the

total amount of days' supply obtained during a specific period of time divided by the number of days in the observation period. A PDC is calculated as the total number of days with medication available during a specific period of time divided by the number of days in the observation period.(23) The difference between these two calculations is that PDC caps the calculation at 1.0 (all days in the observation period have medication available); whereas the MPR can be unreasonably elevated above 1.0 if the total days supplied exceeds the observation period. This can occur if medication dispensations are obtained earlier, or an individual is stockpiling medications (e.g., preparing for a trip).(27) Since the MPR can produce a skewed measurement, the PDC is a preferred measure of adherence.

The PDC is used as a tool to measure health care quality and is endorsed by multiple national organizations, including Centers for Medicare and Medicaid Services, National Quality Forum, and Centers for Disease Control and Prevention.(28) It also has reasonable agreement with other indirect measures of adherence, including patient interviews, pill counts, and clinician assessments.(28-30) Lastly, PDC is the leading method of measure for calculating adherence using administrative data.(31)

1.1.5 Proportion of Days Covered by Multiple Medications

The PDC has been used to assess adherence to individual medications or medication classes. In real world clinical settings, individuals with chronic conditions often require polypharmacy, which can also include switching between medications and medication classes. These medication-taking behaviors are inadequately captured by measuring adherence to a single medication. The idea of determining adherence to multiple medications has gained popularity by clinicians and stakeholders.

Calculating adherence to multiple medications has been utilized in studies ranging from examining secondary prevention medications in post myocardial infarction patients(32), to exploring the effects of medication copayments on adherence.(33) These studies recognize the importance of capturing adherence in a clinically sensible manner, reflecting the complexity of underlying treatment patterns (e.g., tapering, titration or augmentation) that is involved in delivering individualized care. A study undertaken by Chapman and colleagues highlights the substantial risk of adverse cardiovascular events in individuals with hypertension and dyslipidemia associated with poor adherence across many medication classes that is not well understood given previous studies have focused on analyzing adherence to a single medication or medication class.(34) They suggest measuring adherence to multiple medications produces more practical implications for clinicians and decisions makers responsible for treating chronic diseases. Although there are no published guidelines on how to conduct these measurements, Choudhry and colleagues suggest one method to examine adherence to multiple medications is by calculating the proportion of days during which patients have at least 1 of their medications available to them.(35) This definition would capture individuals on multiple medications that may have substantially unique patterns of adherence.

1.1.6 Dynamic Measure of Adherence: Group Based Trajectory Modelling

Adherence presents as a complex pattern that can change over time. For example, an individual initiating therapy with a new medication may begin with nearly perfect adherence (PDC=1.0) but may gradually reduce the frequency of taking their medications. Measures such as PDC provide an average adherence rate over a period of time and therefore will not be sensitive to changes in adherence patterns within the observation period.(36, 37)

A new and more dynamic approach to assessing adherence is group-based trajectory modelling.(38) Group-based trajectory modeling was first developed to identify common patterns of behavior in a group.(39) This methodology has been successfully applied to medication adherence and can be used to stratify individuals into different patterns of medication use over time.(36, 37)

A trajectory model provides estimated probabilities of group membership for each individual and a trajectory curve over time for each adherence group.(36) Given that poor adherence to medications is associated with poor clinical outcomes, increased hospitalizations and healthcare costs (40-42), the use of such models can help us better understand adherence in order to improve patient care and outcomes.

1.1.7 Type 2 Diabetes, Depression and Adherence

Those with diabetes have a two-fold increased risk of depression compared to the general population without diabetes.(43) Depression affects 1 in 5 individuals with type 2 diabetes.(15, 44, 45) Among individuals with type 2 diabetes, depression is associated with a two-fold increase in mortality.(46) Ultimately, depression affects more than just mood and can influence daily functioning by causing lethargy or decreasing motivation to maintain one's health.(47-49) Diabetes places a significant self-management burden on individuals and good adherence to pharmacological and non-pharmacological therapies is required to achieve optimal blood glucose control and lower risk of serious complications.(25) Literature suggests that depression is associated with a decline in diabetes self-care activities, including diet and exercise, and poor adherence to antihyperglycemic medications.(16, 50, 51)

Depression is a well-known risk factor for poor adherence to oral antihyperglycemic medications in individuals with type 2 diabetes.(Table 1.1) However, the majority of studies

examining the association between depression and adherence to oral antihyperglycemic medications are cross-sectional and conceptualize depression as a static variable at one point in time when examining its association with diabetes.(16, 51, 54, 56-58, 60, 62, 64, 66, 67, 69-74, 76, 79-81, 83-90, 93) Unfortunately, identifying depression can be challenging and clinically relevant symptoms may be present well before a clinician establishes the diagnosis.(94, 95) Little is currently known about how antihyperglycemic adherence is impacted during this time period.

Given that individuals with diabetes and depression are at three-fold higher risk of poor adherence to oral antihyperglycemic medications compared to individuals with diabetes alone (15, 48), a better understanding on the progression of depression leading up to a diagnosis and the association with adherence to antihyperglycemic medications is necessary in order to better care for those living with diabetes. Gonzalez and colleagues found a continuous relationship between symptoms of depression and non-adherence to management of diabetes.(15) Evidence showed that even mild symptoms of depression that did not meet the criteria for a diagnosis of major depressive disorder had a detrimental impact on optimizing management of diabetes.(15) Other studies have suggested the need for future research with longitudinal studies to identify the pathways that contribute to the association between depression and adherence to antihyperglycemic medications.(49, 61, 96)

Another important factor to consider in the association between depression, diabetes and adherence is the treatment of depression. Remission is the primary goal of treatment for depression to avoid impairment in daily activities.(20) In the case of diabetes, as discussed above, such impairments can prevent an individual from following the necessary diet and exercise requirements needed to manage diabetes, as well as adhere to necessary medications.(9, 96)

Although effective treatments for depression exist, there is limited research examining the association between treated depression and adherence to antihyperglycemic medications.(68, 97) It is possible that studies have overlooked how adherence patterns to antihyperglycemic medications may shift as a result of achieving control of depressive symptoms or remission.

1.2 Thesis Objectives

The intent of this thesis is two-fold, with a focus on evaluating adherence to oral antihyperglycemic medications in patients with comorbid depression. The objectives of this thesis were 1) determine if symptoms of depression occurring before a diagnosis is recorded are associated with poor medication adherence, 2) examine the impact of depression treatment on adherence to oral antihyperglycemic medication therapy in individuals with diabetes and a new episode of depression.

1.3 Specific Objectives and Thesis Outline

Chapter 2: a retrospective cohort study analyzing depression and antecedent medication adherence to oral antihyperglycemic medications in a cohort of new metformin users with a new depressive episode compared to controls with a pseudo depressive episode date.

Chapter 3: a retrospective cohort study analyzing depression and subsequent medication adherence to oral antihyperglycemic medications in a cohort of new metformin users with a new depressive episode on antidepressant treatment compared to controls who did not receive treatment.

Chapter 4: the overall summary, opportunities for future research and clinical implications of this thesis.

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Table 1.1 Studies of the Association Between Depression and Adherence to Oral Antihyperglycemic Medications in Individuals with Type 2 Diabetes.

Reference	Study Design	Depression Criteria	Adherence Criteria
McKellar et al., 2004(61)	Cohort study Depression at baseline Adherence measured over follow-up	Centers for Epidemiologic Studies Depression Scale	4-item Morisky Medication Adherence scale
Kilbourne et al., 2005(75)	Cohort study Depression at baseline Adherence measured over follow-up	Patient Health Questionnaire-9	Electronic Monitoring Caps
Hill-Briggs et al., 2005(82)	Cohort study Depression at baseline Adherence measured over follow-up	Centers for Epidemiologic Studies Depression Scale	4-item Morisky Medication Adherence scale
Kalsekar et al., 2006(7)	Cohort study Depression at baseline Adherence measured over follow-up	International Classification of Diseases (ICD) ninth revision (ICD-9) codes	Medication Possession Ratio
Kalsekar et al., 2006(59)	Cohort study Depression at baseline Adherence measured over follow-up	International Classification of Diseases (ICD) ninth revision (ICD-9) codes	Medication Possession Ratio
Gonzalez et al., 2008(91)	Cohort study Depression at baseline Adherence measured over follow-up	Harvard National Depression Screening Scale	Summary of Adherence to Diabetes Self Care Activities
Katon et al., 2009(9)	Cohort study Depression at baseline Adherence measured over follow-up	Patient Health Questionnaire-9	Continuous Medication Gap-medication refill gaps for ≥20% of days covered for medications prescribed
Dirmaier et al., 2010(65)	Cohort study Depression at baseline Adherence measured over follow-up	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition criteria	Self-report to 1 assessment question

		for depression and International Classification of Diseases (ICD) tenth revision (ICD-10) codes	
Caughey et al., 2013(68)	Cohort study Depression at baseline Adherence measured over follow-up	N/A, focus on antidepressant use	N/A, focus on persistence
Gonzalez et al., 2016(92)	Cohort study Depression at baseline Adherence measured over follow-up	Validated self-reports for diabetes distress and depression and semi-structured depression interviews	Electronically Monitoring Caps and Validated Self-Reports
Axon et al., 2016(55)	Cohort study Depression at baseline Adherence measured over follow-up	International Classification of Diseases (ICD) ninth revision (ICD-9) codes	Medication Possession Ratio
Lunghi et al., 2017(78)	Cohort study Depression at baseline Adherence measured over follow-up	International Classification of Diseases (ICD) ninth revision (ICD-9) and the tenth revision (ICD-10) codes	Proportion of Days Covered
Lunghi et al., 2017(98)	Cohort study Depression at baseline Adherence measured over follow-up	International Classification of Diseases (ICD) ninth revision (ICD-9) and the tenth revision (ICD-10) codes	Proportion of Days Covered
Bauer et al., 2017(63)	Cohort study Depression at baseline Adherence measured over follow-up	Patient Health Questionnaire-8	Pharmacy utilization data to identify nonadherence as medication never dispensed or dispensed once and never refilled and New Prescription Medication Gap

Lunghi et al., 2017(52)	Cohort study Depression as time-dependent variable Measured time to discontinuance	International Classification of Diseases (ICD) ninth revision (ICD-9) or the tenth revision (ICD-10) codes	N/A, focus on persistence
Kostev et al., 2018(53)	Cohort study Depression at baseline Adherence measured over follow-up	International Classification of Diseases (ICD) tenth revision (ICD-10) codes	N/A, focus on persistence
Wilson et al., 1986(87)	Cross-sectional study	Beck Depression Inventory & Centers for Epidemiologic Studies Depression Scale (average of the 2)	Diabetes Daily Care Questionnaire
McCaul et al., 1987(17)	Cross-sectional study	Automatic Thoughts Questionnaire	Interviews
Ciechanowskiet al., 2000(16)	Cross-sectional study	The Hopkins Symptom Checklist-90	Interruptions of medication treatment defined by an episode in which a refill or subsequent prescription of oral hypoglycemics was overdue by more than 15 days and by more than 25% of the intended duration of use
Herpertz et al., 2001(56)	Cross-sectional study	Beck Depression Inventory	Interviews
Kuo et al., 2003(79)	Cross-sectional study	Centers for Epidemiologic Studies Depression Scale	Interviews

Lin et al., 2004(88)	Cross-sectional study	Patient Health Questionnaire-9	Pharmacy Database
Park et al., 2004(51)	Cross-sectional study	Centers for Epidemiologic Studies Depression Scale	Questionnaire
Weijman et al., 2005(73)	Cross-sectional study	Centers for Epidemiologic Studies Depression Scale	Multidimensional Diabetes self-management Checklist
Chao et al., 2005(81)	Cross-sectional study	Patient Health Questionnaire-8	4-item Morisky Medication Adherence scale
Nau et al., 2007(69)	Cross-sectional study	Patient Health Questionnaire-8	Questionnaire
Mann et al., 2009(84)	Cross-sectional study	Patient Health Questionnaire-9	4-item Morisky Medication Adherence scale
Zhang et al., 2013(57)	Cross-sectional study	Chinese version of the Diabetes Distress Scale	Revised treatment Adherence in Diabetes Questionnaire
Sweileh et al.,2014(86)	Cross-sectional study	Beck Depression Inventory	8-item Morisky Medication Adherence scale
Jackson et al., 2015(83)	Cross-sectional study	Self-report	8-item Morisky Medication Adherence scale
Kim et al., 2015(90)	Cross-sectional study	Structured questionnaires	Structured questionnaires

Chew et al., 2015(54)	Cross-sectional study	Patient Health Questionnaire-9	8-item Morisky Medication Adherence Scale
Weidenbacher et al., 2015(71)	Cross-sectional study	Mental Health Inventory (MHI)-5	Survey
Chew et al., 2015(64)	Cross-sectional study	Patient Health Questionnaire-9	8-item Morisky Medication Adherence Scale
Li et al., 2017(72)	Cross-sectional study	Centers for Epidemiologic Studies Depression Scale	Interviews
Gentil et al., 2017(76)	Cross-sectional study	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition criteria for depression	Medication Possession Ratio
Mossie, et al.,2017(85)	Cross-sectional study	Beck Depression Inventory	8-item Morisky Medication Adherence scale
Belvederi et al., 2017(80)	Cross-sectional study	21 item Beck Depression Inventory	4-item Morisky Medication Adherence scale
Ellouze et al., 2017(60)	Cross-sectional study	Arabic Hospital Anxiety and Depression Scale	4-item Morisky Medication Adherence scale
Nanayakkara et al., 2018(93)	Cross-sectional study	The Brief Case find for Depression	Interviews
Reach et al., 2018(67)	Cross-sectional study	13-Item Beck Depression Inventory Questionnaire	French 6-item validated Girerd questionnaire

Garcia et al., 2019(58)	Cross-sectional study	Patient Health Questionnaire-8	Proportion of Days Covered
Hoogendoorn et al., (2019)(62)	Cross-sectional study	Patient Health Questionnaire-8	4-item Morisky Green Levine Medication Adherence Scale
Burns et al., 2019(74)	Cross-sectional study	Patient Health Questionnaire-9	2 Question Interview
Chlebowy et al., 2019(89)	Cross-sectional study	Depression, Anxiety and Stress Scale 21	Surveys
Alves Peres et al., 2020(70)	Cross-sectional study	Medical charts	8-item Morisky Medication Adherence scale

CHAPTER 2: Depression and Antecedent Medication Adherence in a Cohort of New Metformin Users

2.1 Introduction

Diabetes is a common chronic condition, with 2.8 million Canadian adults (10.1% of the population) living with diabetes in 2019.(1) Type 2 diabetes accounts for 90% of those with diabetes and often requires antihyperglycemic medications to achieve and maintain blood glucose targets.(1, 2) Good adherence to antihyperglycemic medications contributes to optimal blood glucose control and is associated with a lower risk of diabetes complications.(3, 4)

Depression is present in up to 30% of individuals with diabetes and is a well-known risk factor for poor medication adherence.(5, 6) Studies examining the relationship between depression and adherence to oral antihyperglycemic medications are either cross-sectional or measure adherence following depression diagnosis.(7-13) However, symptoms of depression precede clinical diagnosis and could affect medication adherence earlier than currently reported.(14, 15) Adherence rates can change over time and reduced willingness or capacity to take medication may facilitate identification of individuals whose medication use is influenced by underlying symptoms of depression. If true, poor medication adherence could be an indicator that guides clinicians to assess for signs of depression. This could allow for earlier interventions to manage depression that may reduce subsequent sequalae (or the cascade effect) of non-adherence to antihyperglycemics.(13)

The overarching goal was to determine if medication adherence is affected in the time before a depressive episode. The first objective was to characterize adherence to oral antihyperglycemic medications in the year before a depressive episode using a traditional proportion of days covered (PDC)(16) approach and group-based trajectory modelling (GBTM).(17) The second objective was to examine the association between depression and

medication adherence. I hypothesized that individuals with a depressive episode would be more likely to have poor adherence in the preceding year compared to controls who did not experience a depressive episode.

2.2 Participants and Methods

2.2.1 Population and setting

Administrative health data from Alberta, Canada between April 1, 2008 and March 31, 2018 were used to conduct a population-based retrospective cohort study. Alberta Health databases used for this study included the Population Registry, which contains demographic information; the Pharmaceutical Information Network, which has information on all prescription medication dispensations; Practitioner Claims, which has information on all clinician service visits; Ambulatory Care, which captures emergency department visits and day procedures; and the Discharge Abstract Database, which contains information on all hospitalizations. Alberta Health's administrative databases are used to record health service utilization and reimburse healthcare providers under a universal healthcare system. This record system enables health research to be conducted on a vast amount of administrative data. Studies examining the accuracy of coding support the integrity and validate the use of this administrative data source for health research.(18, 19) The University of Alberta Health Research Ethics Board approved the study protocol (Pro00066037).

A standard new user definition was used to create the study group.(20) Individuals 18 years of age and older dispensed metformin as their first antihyperglycemic medication after a minimum one-year washout were considered new metformin users. Women with a health service claim for polycystic ovarian syndrome using metformin as the only antihyperglycemic medication were excluded because it is unlikely metformin was used to treat type 2 diabetes.

2.2.2 Exposure assessment

Individuals who develop a depressive episode exhibit depressive symptoms before the first health service record in an administrative database.(14, 15) These prodromal symptoms may influence medication adherence behavior. Therefore, the exposure of interest was individuals with a new depressive episode and the one-year period prior to diagnosis.(Figure 2.1) A validated definition was used to identify individuals with depression using International Classification of Diseases (ICD) codes (Table 2.1) in the Practitioner Claims, Ambulatory Care, and Discharge Abstract Database.(21) A depressive episode was defined as the first service record for depression occurring at least one year after initiating metformin therapy. The minimum one-year interval between first metformin dispensation and first service record for depression fulfilled three objectives for the study. First, the one-year washout period decreased the likelihood of including individuals with a prevalent depressive episode. Second, it provided an observation window to examine if symptoms of depression occurring before the first service record for depression influence health behaviour. Third, it was sufficiently long enough to calculate an adherence rate (see Outcome sub-section below).

New metformin users with no service records for depression were eligible to be controls in the study. The methods used to define the exposure group, however, could introduce immortal time bias if duration of time before a depressive episode was not accounted for in the control group.(22)(40) To minimize risk of this bias, a depression diagnosis date was randomly assigned using the hot deck approach.(22)(23) The 'missing' depression date for a control was randomly selected from a subgroup of exposed group members who had a similar duration of follow up. If the assigned depression date was less than 1 year after starting metformin or exceeded the control individual's study exit date, the date was dropped and the process repeated. This process created comparable intervals between metformin initiation and a real or pseudo depression date.

2.2.3 Outcome measures

The outcome was adherence to oral antihyperglycemic medications, defined as the proportion of days covered (PDC) during the one-year period before the depression date.(Figures 2.1 and 2.2) An algorithm was constructed to calculate the proportion of days that a participant had at least 1 of their antihyperglycemic medications available to them.(24, 25) First, days that had medication available were identified based on the dispense date and days of supply for each antihyperglycemic medication class. Second, this information was combined for each participant to identify the days that had at least 1 antihyperglycemic medication. For example, for a participant treated with metformin and a sulfonylurea, the day was considered covered if either or both medications were available.(Figure 2.2) Prior to calculating a PDC, the duration of any hospitalization was excluded from the numerator and denominator. Hospitalizations were treated as immeasurable time because administrative health databases do not record inpatient medication use.(26) Last, PDC was calculated by dividing the total number of days with medication available, by the observation interval.

A similar approach was used to calculate a PDC for each 30-day interval within the same time period. A missing value was generated if the length of hospital stay during the observation period was ≥15 days and mean imputation was used to replace missing data.

2.2.4 Covariables

Variables that may impact the association between depression and adherence were identified during the baseline period, which ended on day 366 before the depression date.(Figure 2.1) Sociodemographic information was determined on day 366 before the depression date. Diagnostic codes for health service claims were reviewed to identify a predefined list of chronic conditions.(27)(Table 2.2) In addition, pre-existing diabetes-related complications and mental

health conditions were identified using validated definitions where available.(Table 2.2.) A baseline hemoglobin A1c (HbA1c) was defined as the measurement closest to, but no more than 90 days from, the date 366 days before the depression date. Cardiovascular medications, antihyperglycemics (excluding metformin), and medications used for other chronic conditions were identified from dispensation records in the time period 731 to 366 days before the depression date.(Table 2.3 and Figure 2.1) Last, the number of hospital admissions and practitioner claims were counted in the time period 731 to 366 days before the depression date.

2.2.5 Statistical analyses

The first approach was to conduct a traditional analysis of the association between depression and adherence. Baseline characteristics between exposure and control groups were compared using t-tests and chi square tests for continuous and categorical variables, respectively. A multivariable logistic regression model was used to determine if depression was independently associated with poor adherence. A PDC threshold of <80% was chosen to define poor adherence based on existing literature assessing oral antihyperglycemic medication adherence with claims databases.(28, 29) The multivariable model was constructed by first including all variables with reasonable univariate associations ($p<0.1$) with poor adherence. The model was refined by conducting backward elimination with a criterion of $p>0.1$ to remove a variable from the model. Collinearity was assessed using the variance inflation factor (VIF), with a value >10 indicating variable refinement was required. The adjusted odds ratio and 95% confidence interval were examined to identify factors that were independently associated with poor adherence.

The second approach utilized GBTM to identify different patterns of adherence in the year before the depression date. The 30-day PDC was modelled using a censored normal distribution, months before the depression date as the time variable, and all covariables included

in the final multivariable model defined in the first approach. Monthly windows were chosen because the median days supplied for all antihyperglycemic medications in the dataset was 30 days. A two stage selection process was followed as recommended by Nagin and colleagues to identify the model that best fit the data.(17) In the first stage, models were estimated with 2 to 6 groups and all trajectories calculated using a quadratic equation. The model with 5 groups generated a maximum Bayesian information criterion score and at least 5% of the study sample in each group. In the second stage, linear, quadratic, and cubic polynomial equations were examined to calculate the shape of each trajectory. The final model that best defined each trajectory used cubic polynomials, which was expected because adherence trajectories are often non-linear.(30)

All analyses were conducted using Stata 16 (StataCorp LP, College Station, TX, USA). The PDC variable was calculated using de novo code that was based, in part, on a published method.(31) The trajectory models were created using the trajectory plug-in for Stata.(32)

2.2.6 Sensitivity Analyses

First, analyses were replicated using all covariables in the models. Second, the baseline HbA1c was included in the multivariable models to further account for disease severity of diabetes. A1c was not available for all participants in the study; therefore, analyses were conducted on the subgroup with an available A1c. Third, ICD codes were removed for recurrent depression from the definition used to identify a depressive episode. Since depression is a recurring and remitting disease, it was difficult to be certain that individuals identified with codes for recurrent depression were experiencing a new episode, or an ongoing episode that had not been previously documented in the administrative health records.(33) The last sensitivity analysis excluded participants who received dispensations with 7, 14, or 28 days supplied for all

records because it is likely these individuals were using adherence aids, like blister packaging or dosettes.

2.3 Results

2.3.1 Baseline characteristics

Between April 1, 2008 and March 31, 2018, 214,762 individuals were dispensed an oral antihyperglycemic medication and 165 056 (77%) were adult new metformin users.(Figure 2.3) A total of 31,517 (20%) new metformin users had healthcare records for depression after starting metformin and 17,418 (10.6%) had their first depression-related service record a minimum of one year after starting metformin. The mean duration between metformin initiation and a depressive episode was 2.7 (SD 1.7) years. A depression date was randomly assigned to 114,181 controls. There were 19,358 eligible controls who did not have a viable pseudo depression date because the randomly assigned date was either within 1 year of starting metformin or exceeded their study exit date. The mean number of medications and comorbidities at baseline was higher for the depression group compared to controls.(Table 2.4) Participants with depression had a higher proportion of hospitalizations, clinician visits and were more likely to have service claims for anxiety and brain diseases (Alzheimer's, dementias) than controls.

2.3.2 Proportion of Days Covered in Year Before Depression

The PDC in the year before the depression date was lower for participants with a depressive episode (0.61 [SD 0.39]) compared to controls (0.63 [SD 0.38]) ($p<0.001$). More participants with depression (9,382, 54.0%) had poor adherence compared to controls (58,731, 51.5%) ($p<0.001$). After adjustment in the multivariable analysis, participants with a depressive episode were more likely to have poor adherence compared to controls (adjusted odds ratio 1.21; 95%CI 1.17,1.26).

2.3.3 Adherence Trajectories

The trajectory with the largest group of participants (34.8%) was nearly perfect adherence (PDC>0.95) throughout the one-year period before the depression date.(Figure 2.4, Table 2.5) There was a substantial proportion of participants (18.3%) who stopped using oral antihyperglycemic medications prior to the 1-year study period (PDC=0 throughout). For two trajectory groups, the mean PDC started at 0.75 then declined either rapidly to 0 within 4 months of the depression date (9.2% of participants) or gradually to a mean PDC of 0.65 (30.1% of participants). The remaining trajectory (7.6% of participants) started at a mean PDC of 0.26 and ended at a mean PDC of 0.58. Participants with a depressive episode were more likely to be in one of the four trajectories of poor adherence compared to controls (adjusted odds ratio 1.24; 95% CI 1.19-1.29).

2.3.4 Sensitivity Analyses

The multivariable model including all covariables, as well as, the multivariable logistic regression model using data from the 74,586 (56.7%) participants with a baseline HbA1c both produced adjusted odds ratios that were similar in magnitude, direction, and statistical significance to the main logistic regression model.(Table 2.6) The trajectories from both of these sensitivity analyses were also consistent with the main trajectory results.(Figures 2.5 and 2.6)

There were 191 (0.1%) participants identified using ICD codes for recurrent depression and 3,976 (3.0%) participants who appeared to be using adherence aids. Analyses conducted after excluding these individuals produced adjusted odd ratios that were similar in magnitude, direction, and statistical significance to the main logistic regression model.(Table 2.6) The adherence trajectories were also consistent with the main trajectory results.(Figures 2.7 and 2.8)

2.4 Discussion

This study examined medication adherence in the year before a depressive episode in a cohort of new metformin users. Participants with a depressive episode were 1.21 times more likely to have poor adherence to metformin in the year before that episode compared to those who never had a depressive episode. Using GBTM, 4 trajectories of poor adherence were identified and one trajectory of good adherence to metformin in the year before a depressive episode. Participants with a depressive episode were 1.24 times more likely to belong to trajectories of poor adherence compared to controls. These findings are consistent with the hypothesis that people with a depressive episode would be more likely to have poor adherence in the preceding year.

Several studies have examined the association between depression and adherence to oral antihyperglycemic medications.(7-13) However, there are consistent methodologic elements among these studies that limit the understanding of the relationship between depression and medication adherence. For example, almost all studies identified prevalent depression at a fixed point in time and none of these studies collected information to characterize duration of depression. Many studies were cross sectional and measured concurrent medication adherence with self-reported surveys. Only a few studies used pharmacy refill data to measure adherence following the identification of depression.(9, 10)

Lunghi and colleagues report the only study to examine the association between a new depressive episode and subsequent adherence to oral antihyperglycemic medications.(12) Like the study, Lunghi and colleagues used a claims-based definition to identify a new depressive episode, though they also included antidepressant medication dispensations in their exposure definition. They observed a significant association between a new depressive episode and

subsequent occurrence of poor adherence (adjusted odds ratio: 1.24; 95% CI: 1.13–1.37).(12) Consistency between their study and this one, regardless of the different observational periods, highlight the need to understand how evolving symptoms of depression can affect antihyperglycemic medication use.

This study extends the understanding of the relationship between depression and medication adherence. First, the relationship in an observation period that has not been reported previously was examined. The observation supports the hypothesis that clinically relevant symptoms are present before the first claims record for depression and therefore affect medication adherence earlier than previously reported.(14, 15) Second, the use of GBTM identified five distinct adherence trajectories with slopes that changed over time. The variability in these trajectory patterns confirms the need to consider adherence as a dynamic process that cannot be captured by static measures or averages calculated over long observation intervals. In addition, most of the observed trajectories showed a decrease in adherence over time, which is consistent with previous studies investigating the predictive properties of adherence trajectories.(30)

The findings that poor adherence occurs before a depressive episode could prompt clinicians to consider screening for depressive symptoms in individuals with poor adherence. There are several validated surveys that could be used when investigating the potential causes of poor adherence.(10, 34, 35) Ultimately, early recognition and intervention of depressive symptoms may facilitate the improvement of adherence. This can have important implications on diabetes management since poor adherence to antihyperglycemic medications is associated with a higher risk of adverse clinical outcomes.(4, 36) Consequently, improving adherence can reduce the risk of complications, decrease health care costs and increase quality of life.(13)

Important strengths of this study are the use of a validated case definition of depression and real-world claims data to assess the association between depression and poor adherence. The minimum one-year washout period improved the likelihood of identifying individuals with a new episode of depression rather than individuals with prevalent depression of unknown duration. Use of depression diagnosis-time matching for the control group reduced the risk of immortal time bias by ensuring adherence was measured within similar durations of diabetes between the two study groups.(22) Using the "at least one" definition when calculating PDC by multiple medications allowed for an individual to be considered adherent regardless if they discontinued one of their medications and were adherent to the other. Last, the observed association between depression and adherence remained consistent in magnitude, direction, and statistical significance when using different approaches to characterize adherence and in the sensitivity analyses.

There are also several important limitations to consider when interpreting the observations. First, depression is often under-diagnosed and under-reported, which could have led to an underestimation of the number of individuals with depression.(37) To mitigate this risk of misclassification, an accepted case definition was used that has high positive (92%) and negative (91%) predictive values.(21) Second, I was unable to determine severity of the depressive episode. Although ICD coding does enable reporting disease severity in the first (ICD-10) and second (ICD-9) decimal place, administrative databases, like the one used in this study, do not regularly record this level of detail. Furthermore, if this information was available, there are currently no reliable algorithms to stratify individuals by disease severity using claims-based data. Administrative data provides no clinical information on symptoms that may impact a person's diagnosis, or the duration of time symptoms may be present prior to diagnosis. Third, as

with other studies using prescription refill information, it was assumed a dispensation record was a surrogate marker for the individual actually consuming the medication. This creates a well-known overestimation of medication adherence. However, PDC is the leading method used to calculate medication adherence in administrative databases and it is widely accepted as having reasonable agreement with other measures like patient interviews, pill counts and clinician assessments.(16, 38, 39)

2.5 Conclusion

Individuals with a depressive episode were more likely to have poor adherence in the preceding year. These results suggest that depressive symptoms may negatively affect medication adherence before a diagnosis of depression is made by a clinician. By following adherence trajectories over 6 to12-month intervals, clinicians may be able to identify people experiencing symptoms of depression earlier. Future studies should examine the impact of depression screening and intervention in people with poor adherence to oral antihyperglycemic medications.

2.6 References

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Table 2.1. International Classification of Diseases (ICD) 9 and 10 Codes Used to Identify Individuals with Depression.

ICD-10-CA Code*	Definition	ICD-9-CM Code†	Definition
F32.0	Mild depressive episode	296.21	Major depressive disorder, single episode- mild
F32.1	Moderate depressive episode	296.22	Major depressive disorder, single episode- moderate
F32.2	Severe depressive episode without psychotic symptoms	296.23	Major depressive disorder, single episode- severe, without mention of psychotic behavior
F32.3	Severe depressive episode with psychotic symptoms	296.24	Major depressive disorder, single episode- severe, specified as with psychotic behavior
F32.4	Depressive disorder, single episode, in partial remission	296.25	Major depressive disorder, single episode- in partial or unspecified remission
F32.5	Depressive disorder, single episode, in full remission		
F32.8	Other depressive episodes		
F32.9	Depressive episode, unspecified	296.20	Major depressive disorder, single episode- unspecified
		311	Depressive disorder, not elsewhere classified
F33.0	Recurrent depressive disorder, current episode mild	296.31	Major depressive disorder, recurrent episode- mild
F33.1	Recurrent depressive disorder, current episode moderate	296.32	Major depressive disorder, recurrent episode- moderate
F33.2	Recurrent depressive disorder, current episode severe without psychotic symptoms	296.33	Major depressive disorder, recurrent episode- severe, without mention of psychotic behavior
F33.3	Recurrent depressive disorder, current episode severe with psychotic symptoms	296.34	Major depressive disorder, recurrent episode- severe, specified as with psychotic behavior

		296.35	Major depressive disorder, recurrent episode in partial or unspecified remission
F33.8	Recurrent depressive disorder, other		
F33.9	Recurrent depressive disorder, unspecified	296.30	Major depressive disorder, recurrent episode- unspecified
F34.1	Dysthymia	300.4	Dysthymic disorder
F41.2	Mixed anxiety and depressive disorder		

*Case Definition 4; †Case Definition 1 in: Fiest KM, et al. BMC Psychiatry 2014;14:289 (Table 1)

Table 2.2. International Classification of Disease (ICD) Codes Used to Identify Comorbidities.

Chronic Condition	Enhanced ICD-9-CM	ICD-10
1. Congestive heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4–425.9, 428.x	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5–I42.9, I43.x, I50.x, P29.0
2. Cardiac arrhythmias	426.0, 426.13, 426.7, 426.9, 426.10, 426.12, 427.0–427.4, 427.6–427.9, 785.0, 996.01, 996.04, V45.0, V53.3	I44.1–I44.3, I45.6, I45.9, I47.x–I49.x, R00.0, R00.1, R00.8, T82.1, Z45.0, Z95.0
3. Valvular disease	093.2, 394.x–397.x, 424.x, 746.3–746.6, V42.2, V43.3	A52.0, I05.x–I08.x, I09.1, I09.8, I34.x–I39.x, Q23.0–Q23.3, Z95.2–Z95.4
4. Pulmonary circulation disorders	415.0, 415.1, 416.x, 417.0, 417.8, 417.9	I26.x, I27.x, I28.0, I28.8, I28.9
5. Peripheral vascular disorders	093.0, 437.3, 440.x, 441.x, 443.1– 443.9, 447.1, 557.1, 557.9, V43.4	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
6. Hypertension	401.x-405.x	I10.x-I13.x, I15.x
7. Paralysis	334.1, 342.x, 343.x, 344.0-344.6, 344.9	G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0–G83.4, G83.9
8. Other neurological disorders	331.9, 332.0, 332.1, 333.4, 333.5, 333.92, 334.x–335.x, 336.2, 340.x, 341.x, 345.x, 348.1, 348.3, 780.3, 784.3	G10.x–G13.x, G20.x–G22.x, G25.4, G25.5, G31.2, G31.8, G31.9, G32.x, G35.x–G37.x, G40.x, G41.x, G93.1, G93.4, R47.0, R56.x
9. Chronic pulmonary disease	416.8, 416.9, 490.x –505.x, 506.4, 508.1, 508.8	I27.8, I27.9, J40.x–J47.x, J60.x-J67.x, J68.4, J70.1, J70.3
10. Diabetes	250.x	E10.x-E14.x
11. Hypothyroidism	240.9, 243.x, 244.x, 246.1, 246.8	E00.x–E03.x, E89.0
12. Renal failure	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 585.x, 586.x, 588.0, V42.0, V45.1, V56.x	I12.0, I13.1, N18.x, N19.x, N25.0, Z49.0–Z49.2, Z94.0, Z99.2
13. Liver disease	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 456.0–456.2, 570.x, 571.x, 572.2–572.8, 573.3, 573.4, 573.8, 573.9, V42.7	B18.x, I85.x, I86.4, I98.2, K70.x, K71.1, K71.3–K71.5, K71.7, K72.x–K74.x, K76.0, K76.2–K76.9, Z94.4
14. Peptic ulcer disease excluding bleeding	531.7, 531.9, 532.7, 532.9, 533.7, 533.9, 534.7, 534.9	K25.7, K25.9, K26.7, K26.9, K27.7, K27.9, K28.7, K28.9
15. AIDS/HIV	042.x–044.x	B20.x–B22.x, B24.x

16. Lymphoma	200.x–202.x, 203.0, 238.6	C81.x–C85.x, C88.x, C96.x, C90.0, C90.2
17. Cancer	140.x–172.x, 174.x–199.x	C00.x–C26.x, C30.x–C34.x, C37.x–C41.x, C43.x, C45.x–C58.x, C60.x–C76.x, C77.x–C80.x, C97.x
18. Rheumatoid arthritis/ collagen vascular diseases	446.x, 701.0, 710.0–710.4, 710.8, 710.9, 711.2, 714.x, 719.3, 720.x, 725.x, 728.5, 728.89, 729.30	L94.0, L94.1, L94.3, M05.x, M06.x, M08.x, M12.0, M12.3, M30.x, M31.0–M31.3, M32.x–M35.x, M45.x, M46.1, M46.8, M46.9
19. Coagulopathy	286.x, 287.1, 287.3–287.5	D65–D68.x, D69.1, D69.3–D69.6
20. Obesity	278.0	E66.x
21. Weight Loss	260.x–263.x, 783.2, 799.4	E40.x–E46.x, R63.4, R64
22. Fluid and electrolyte disorders	253.6, 276.x	E22.2, E86.x, E87.x
23. Blood loss anaemia	280.0	D50.0
24. Deficiency anaemia	280.1–280.9, 281.x	D50.8, D50.9, D51.x–D53.x
25. Alcohol abuse	265.2, 291.1–291.3, 291.5-291.9, 303.0, 303.9, 305.0, 357.5, 425.5, 535.3, 571.0–571.3, 980.x, V11.3	F10, E52, G62.1, I42.6, K29.2, K70.0, K70.3, K70.9, T51.x, Z50.2, Z71.4, Z72.1
26. Medication abuse	292.x, 304.x, 305.2–305.9, V65.42	F11.x–F16.x, F18.x, F19.x, Z71.5, Z72.2
27. Psychoses	293.8, 295.x, 296.04, 296.14, 296.44, 296.54, 297.x, 298.x	F20.x, F22.x–F25.x, F28.x, F29.x, F30.2, F31.2, F31.5
28. Depression	296.2, 296.3, 296.5, 300.4, 309.x, 311	F20.4, F31.3–F31.5, F32.x, F33.x, F34.1, F41.2, F43.2
Additional Chronic Conditions		
29. Ischemic Heart Disease	410.x-414.x	I20.x-I25.x
30. Stroke	430.x-434.x	I60.x-I64.x
31. Hyperlipidaemia	272.x	E78.x
32. Bipolar Disorder*†	296.0, 296.1, 296.4, 296.5, 296.6, 296.7, 296.8, 296.03, 296.04, 296.10, 296.13, 296.14, 296.40, 296.41, 296.42, 296.43, 296.44, 296.50, 296.52, 296.53, 296.54, 296.60, 296.62, 296.63, 296.64, 296.89	F30-F31
33. Anxiety Disorders*†	294.1, 300.0, 300.2, 300.3, 308.3, 291.89, 292.89, 293.84, 309.81	F40, F41, F42, F410, F411, F413, F418, F419, F429, F431, F430
34. Cerebral Degenerations*†	290, 319, 275.1, 290.3, 291.2, 293.9, 294.1, 294.8, 295.2, 295.9, 331.0, 331.2, 331.0,	G30, G31, G94, G93, F00, F01, F02, F03, F04, F05, F06

	331.1, 331.2, 331.7, 331.8, 292.82, 294.20, 294.21	
35. Nephropathy‡§	580, 590, 584, 587, 591, 593, 753, 403, V45, V56, 996.73, 996.81	I12, I13, N00, N03, N04, N05, N06, N07, N08, N10, N11, N12, N15, N17, N18, N19, N20, N25, N26, N28, Q61, Z91
36. Neuropathy‡§	354, 355, 356, 357, 337.1, 337.9, 277.39, 337.00	G56, G57, G60, G61, G62, G63, G64, G65, G990
37. Amputation ICD Codes	084, 897, 443.8, 443.9, 841.1, 841.2, 841.3, 841.4, 841.5, 841.6, 841.7, 997.2, V49.7, V52.1	Z89, M142, M146
CCP‖/CCI¶ Codes	96.11A, 96.12A, 96.12B, 96.12C, 96.13, 96.14, 96.15, 96.11AA, 96.11PA, 96.12AA, 96.12AB, 96.12AC, 96.12PA, 96.12PB, 96.12PC	1VC91, 1VC93, 1VG93, 1VQ93, 1VX59, 1VX87, 1WA93, 1WE93, 1WJ93, 1WL93, 1WM93, 1WV59.
38. Diabetic Foot Infection‡§	040.0, 680.7, 681.1, 682.7, 707.1, 785.4, 440.24, 730.07, 730.17, 730.27, 730.97	I96, L97, A480, I702, L026, L030, L031, M869, M8617, M8627, M8667
39. Ophthalmic Disorders‡§	379, 362.0, 362.81	H28, H36, H352, H355
40. Hypoglycemia‡§	251, 962.3	E16, T38, E100, E110, E120, E130, E140, E150, E160, E11649
41. Dental‡§	521, 522, 523, 525	K02, K03, K04, K05, K06, K08

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Table 2.3. Cardiovascular Medications and Other Prescription Medications.

Medication	Anatomical Therapeutic Chemical (ATC) Codes
Cardiovascular Medications	
Diuretics	C03
Beta blockers	C07
Calcium channel blockers	C08
Renin-angiotensin system medications	C09
Other Antihypertensives	C02
Digoxin	C01AA05
Antiarrhythmics	C01B
Nitrate	C01DA
Lipid Modifying Medications	C10
Antiplatelets	B01AC
Anticoagulants	B01AA, B01AB
Other Prescription Medications	
Estrogens	G03C
Progestogens	G03D
Estrogens and progestogens in combination	G03F
Antidepressants	N06A
Antipsychotics	N05A
Antianxiety	NO5B
Antiepileptics	N03
Antiparkinson Medications	N04
Opioids	N02A
Proton Pump Inhibitors (PPIs)	A02BC
Butylpyrazolidines	M01AA
Acetic acid derivatives and related substances	M01AB
Oxicams	M01AC
Propionic acid derivatives	M01AE
Fenamates	M01AG
Celecoxib	M01AH
Systemic Glucocorticoids	H02AB

Table 2.4. Baseline Characteristics.

Characteristic*	Participants with Depression n= 17,418	Control Group n= 114, 181	p-Value
Demographics			
Age, years†	56.1 (±15.0)	57.1 (±14.0)	<0.001
Men, n(%)	7,608 (43.7)	67,244 (58.9)	<0.001
Urban Residence, n(%)	14,549 (83.5)	95,230 (83.4)	0.68
Metformin Duration, years†	3.1 (1.8)	2.6 (1.6)	<0.001
Baseline HbA1c			<0.001
%†	7.2 (1.7)	7.3 (1.7)	
mmol/mol†	55 (19)	56 (19)	
Insulin, n(%)	1,349 (7.7)	5,546 (4.9)	<0.001
Number of Medications Other than OAH†	3.7 (±2.4)	2.7 (±2.1)	<0.001
Number of Chronic Conditions†,‡	5.7 (2.8)	`4.6 (2.5)	<0.001
Depression‡, n(%)	8,279 (53.3)	25,779 (22.6)	<0.001
Psychosis‡, n(%)	2,130 (12.2)	3,993 (3.5)	<0.001
Mental Health Disease			
Anxiety Disorders, n(%)	5,283 (30.3)	17,524(15.4)	<0.001
Bipolar, n(%)	676 (3.9)	943 (0.8)	<0.001
Brain Diseases (Alzheimer's, Dementias), n(%)	1,377 (7.9)	4,028 (3.5)	<0.001
Diabetes Complications			
Renal, n(%)	2,752 (15.8)	13,046 (11.4)	<0.001
Neuropathy, n(%)	2,396 (13.8)	10,989 (9.6)	<0.001
Amputations, n(%)	344 (2.0)	1,618 (1.4)	<0.001
Diabetes-related Foot Infections, (n%)	1,684 (9.7)	8,454 (7.4)	<0.001
Ophthalmic, n(%)	2,175 (12.5)	13,101 (11.5)	<0.001
Hypoglycemia, n(%)	468 (2.7)	2,015 (1.8)	<0.001
Dental, n(%)	1,645 (9.4)	8,139 (7.1)	<0.001
Number of Clinician Visits, n(%)			
0	168 (1.0)	2,462 (2.2)	<0.001
1-2	451 (2.6)	5,154 (4.5)	
3-6	1,984 (11.4)	21,173 (18.5)	
≥ 7	14,815 (85.1)	85,392 (74.8)	

Number of Hospitalizations, n(%)			
0	14,829 (85.1)	102,189 (89.5)	<0.001
1-2	2,399 (13.8)	11,298 (9.9)	
≥ 3	190 (1.1)	694 (0.6)	

OAH= Oral Antihyperglycemic Medications
*Values reported as count and percentage
†Values reported as mean and (standard deviation)
‡Chronic conditions as listed by Elixhauser et al.(28)

Table 2.5. Groups Based on Antihyperglycemic Adherence Trajectories in the Year Prior to New Depressive Episode Date.

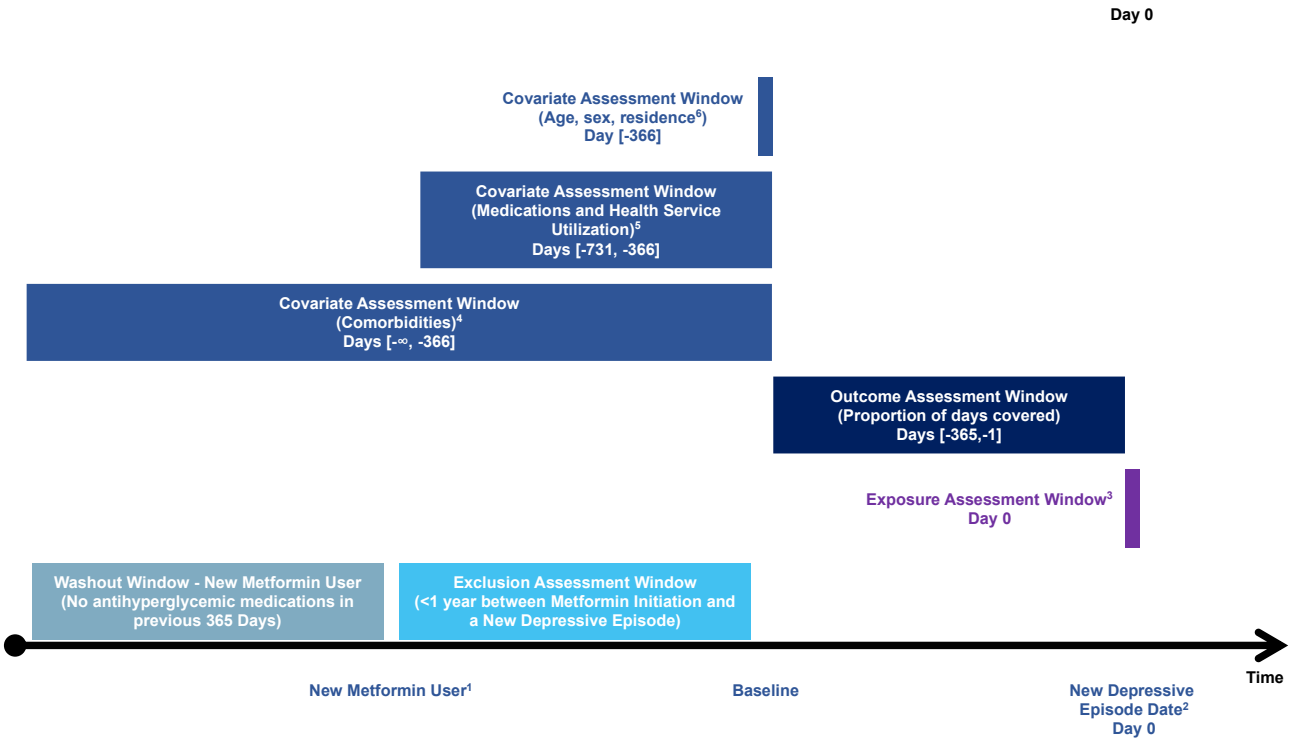
	Trajectory Group					
	1	2	3	4	5	Total
Control Group n(%)	20,292 (17.8)	10,790 (9.5)	8,407 (7.4)	34,339 (30.1)	40,353 (35.3)	114,181
Participants with Depression n(%)	3,598 (20.7)	1,438 (8.3)	1,439 (8.3)	5,091 (29.2)	5,852 (33.6)	17,418
Total	23,890 (18.2)	12,228 (9.3)	9,846 (7.5)	39,430 (30.0)	46,205 (35.1)	131,599

Table 2.6. Logistic Regression Analyses of Poor Adherence in the Year Before the New Depressive Episode Date.

	Adjusted OR (95% CI)*
Main Analysis (n=131,497)	1.21 (1.17-1.26)
Include all covariables (n=131,497)	1.22 (1.18-1.26)
Include baseline haemoglobin A1c value in covariables (n=74,586)	1.20 (1.14-1.26)
Exclude individuals identified using ICD codes for recurrent depression (n=131,688)	1.21 (1.17-1.25)
Exclude individuals who appeared to be using adherence aids (n=127,537)	1.23 (1.19-1.28)

*Covariables included in the model: Age, Sex, Time to Depressive Episode, Number of Antihyperglycemic Medications, Number of Other Chronic Medications, Number of Chronic Medical Conditions (Elixhauser list), Anxiety, Brain Diseases, Renal Disease, Ophthalmic Complications, Neuropathy, Dental Complications, Hospitalizations in preceding year, Clinician Visits in preceding year

Figure 2.1. Study Design – Exposure Group Assignment Based on a New Depressive Episode Occurring At Least 1 Year after Initiating Metformin Therapy.

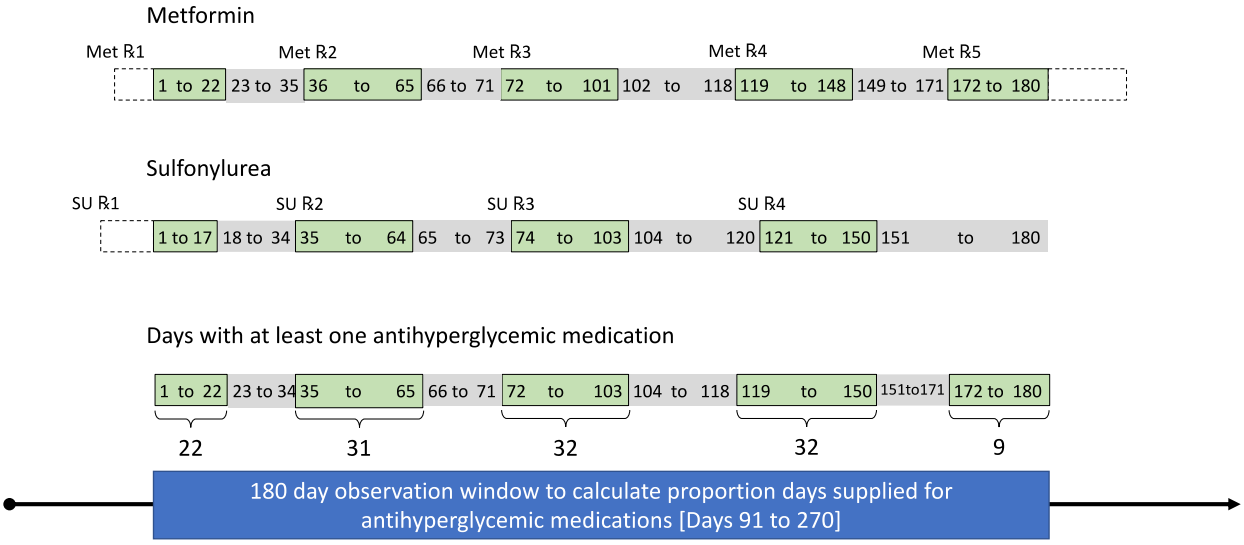


A. Individual considered a New Metformin User based on a minimum of 1 year as a registered beneficiary in Alberta Health, no antihyperglycemic medications (including insulin) dispensed within 1 year before first metformin dispensation, and age ≥18 years on date of first metformin dispensation.
B. Date of first health service record (Practitioner Claim, Ambulatory Care Service, or Hospitalization) for depression [See Table 2.1 for codes]. Controls were randomly assigned a pseudo depression date using the hot deck method for imputing missing data.
C. Exposure group assignment based on health service records: **A New Depressive Episode Group** (first health service record for depression occurs >1 year after initiating metformin); **Control Group** (0 health service records for depression after initiating metformin)
D. Comorbidities included a predefined list of chronic conditions(28), cardiovascular disease, and diabetes-related comorbidities [See Table 2.2 for complete list of comorbidities and codes]. Health service records (Practitioner Claims, Ambulator Care

Service records, and Hospital separations) were reviewed from April 1 of the study individual's enrolment year as a registered beneficiary in Alberta Health until the day before the Outcome Assessment Window.

E. Cardiovascular medications, antihyperglycemic medications (excluding metformin), and other chronic mediations [See Table 2.3 for complete list and codes]. Health services included practitioner claims and hospitalizations. Records were reviewed for the 1-year period before the Outcome Assessment Window.
F. Place of residence was defined as urban or rural based on the Canada Post forward sortation area coding.

Figure 2.2. Example of the Proportion of Days Covered Calculation for a Hypothetical Patient.



This hypothetical individual received 5 dispensations for metformin and 4 dispensations for a sulfonylurea that contributed days supplied within the observation window. Each dispensation provided 30 days supply.

The first relevant metformin dispensation occurred before the start of the observation window and provided coverage for the first 22 days. The remaining dispensations occurred on day 36, 72, 119 and 172 of the observation window.

The first relevant sulfonylurea dispensation occurred before the start of the observation window and provided coverage for the first 17 days. The remaining dispensations occurred on days 35, 74, and 121 of the observation window.

Combining the days covered for both medication classes, identifies (22 + 31 + 32 + 32 + 9) = 126 days covered in the 180-day observation window.

The Proportion Days Covered is 126 ÷ 180 = 0.70.

Figure 2.3. Study Participant Flow Diagram.

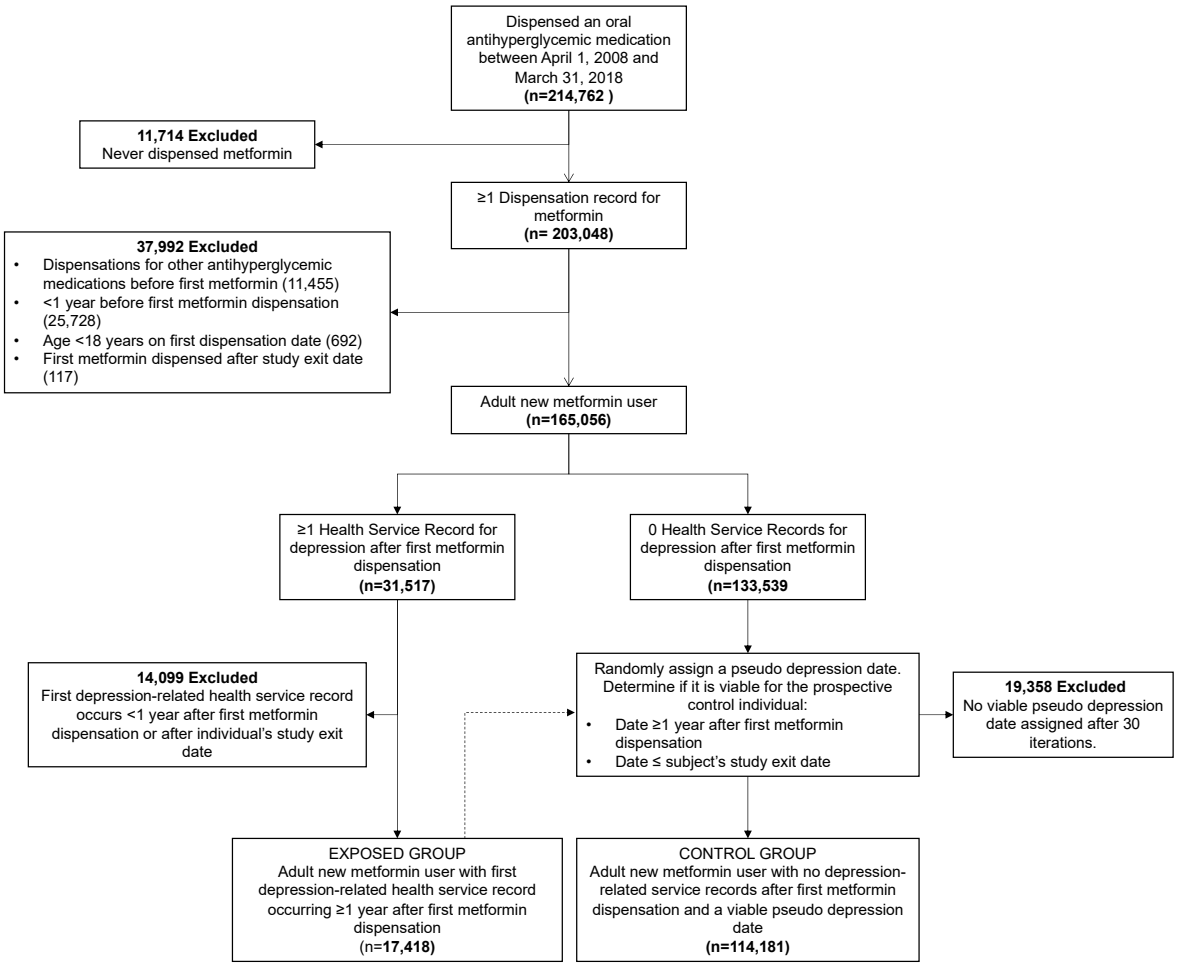
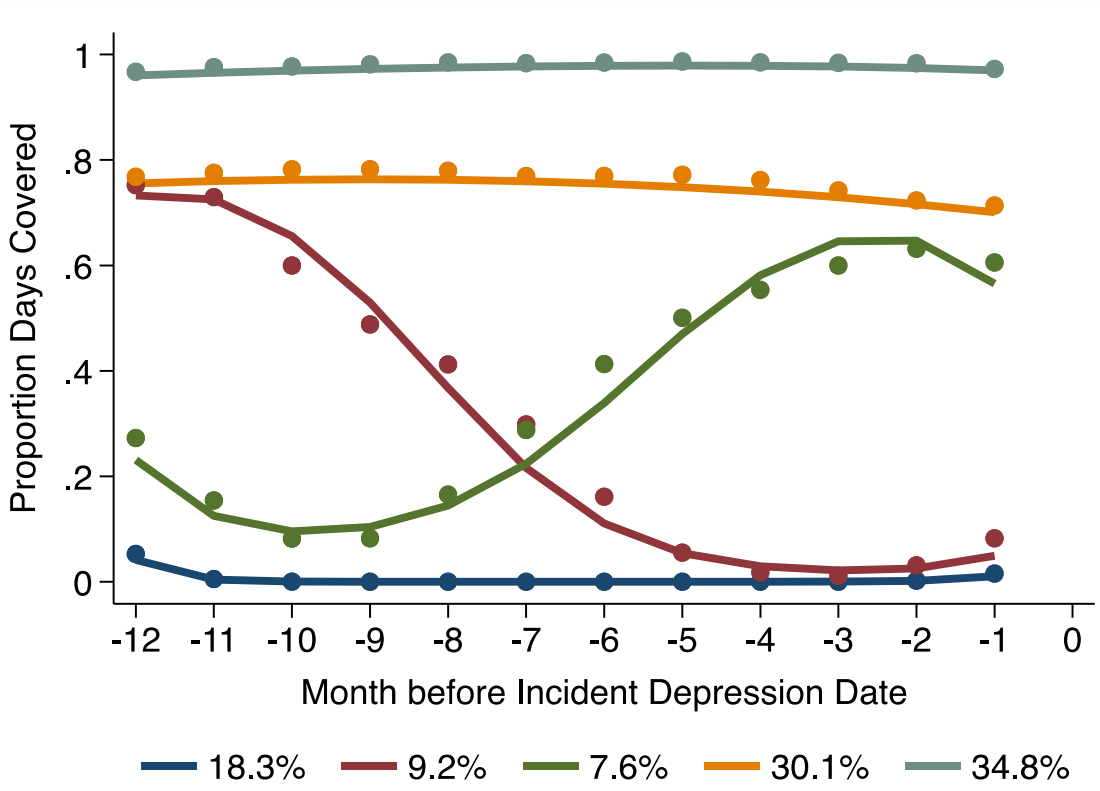
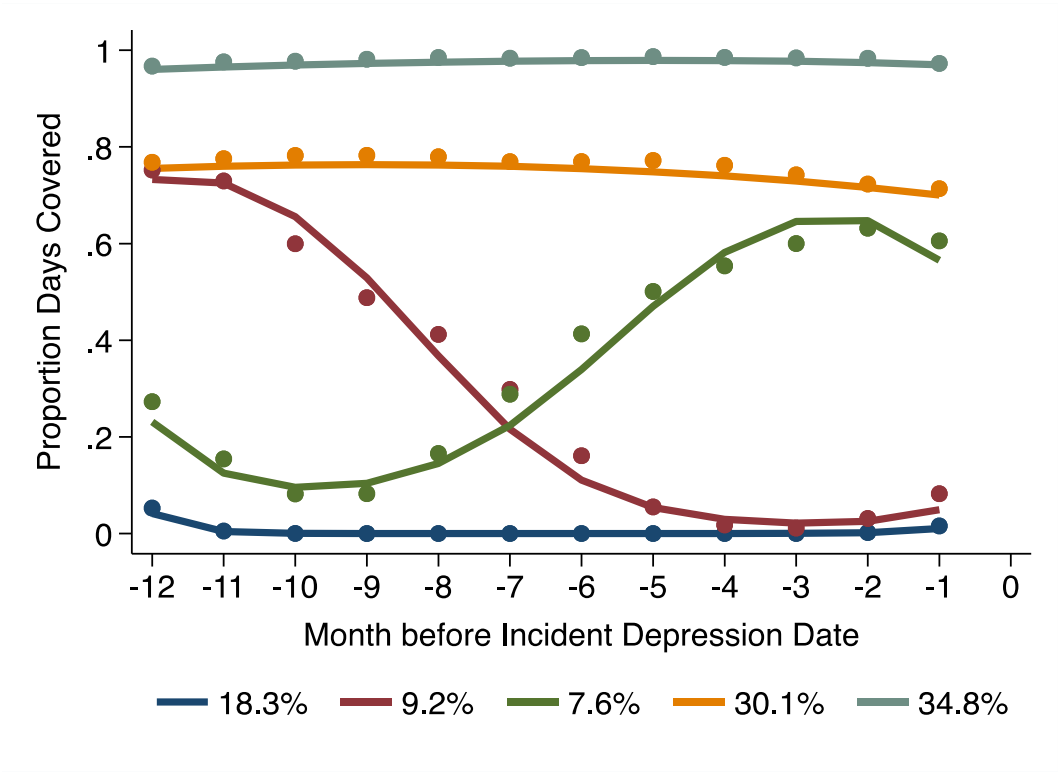


Figure 2.4. Adherence Trajectories in the Year Before a New Depressive Episode – Main Analysis (n=131,599).



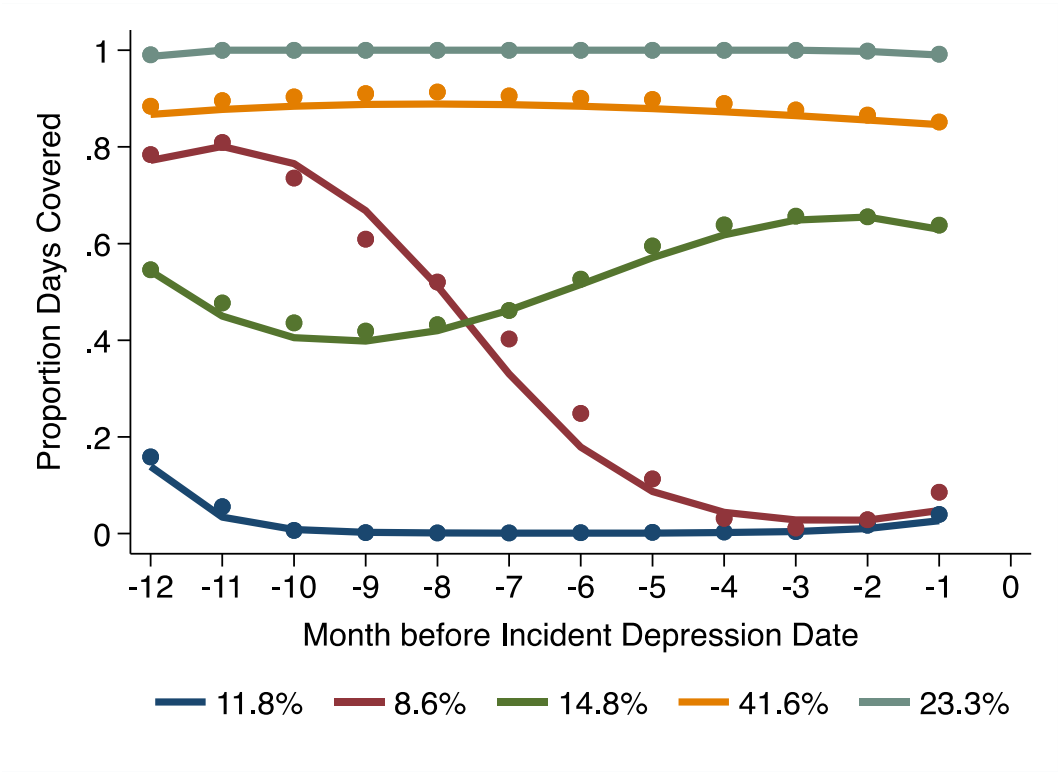
Solid lines represent estimated adherence trajectories, the dot symbols are observed group means of monthly PDC percentages are estimates for each group.

Figure 2.5. Adherence Trajectories in the Year Prior to New Depressive Episode Date – Model Includes all Covariables.



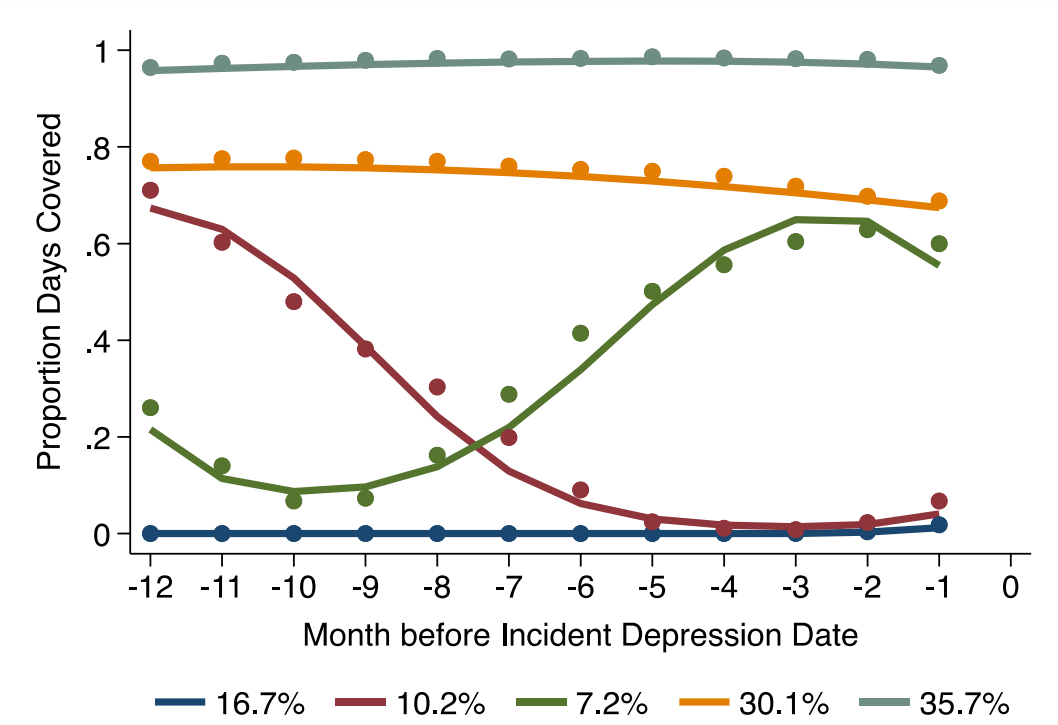
Solid lines represent estimated adherence trajectories, the dot symbols are observed group means of monthly PDC and percentages are estimates for each group.

Figure 2.6. Adherence Trajectories in the Year Prior to New Depressive Episode Date – Subgroup of 74,586 People with a Baseline Hemoglobin A1c.



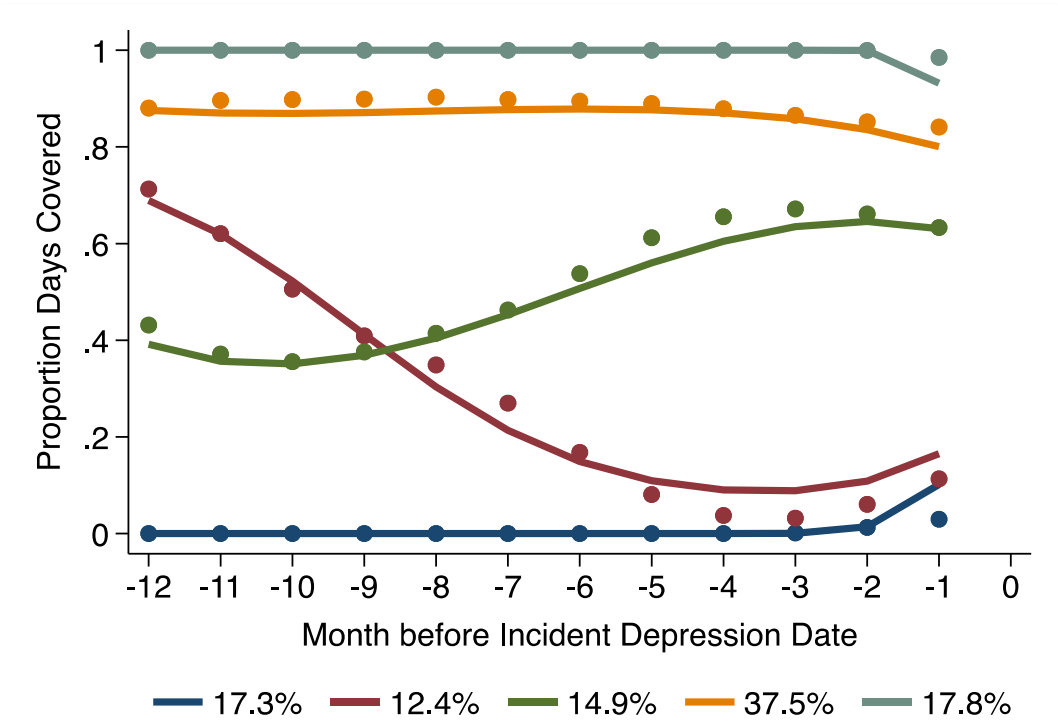
Solid lines represent estimated adherence trajectories, the dot symbols are observed group means of monthly PDC percentages are estimates for each group.

Figure 2.7. Adherence Trajectories in the Year Prior to New Depressive Episode Date – Excludes 191 People Identified Using ICD Codes for Recurrent Depression.



Solid lines represent estimated adherence trajectories, the dot symbols are observed group means of monthly PDC percentages are estimates for each group.

Figure 2.8. Adherence Trajectories in the Year Prior to New Depressive Episode Date – Excludes 3,976 People Likely Using Adherence Aids.



Solid lines represent estimated adherence trajectories, the dot symbols are observed group means of monthly PDC percentages are estimates for each group.

CHAPTER 3: Depression and Subsequent Medication Adherence in a Cohort of New Metformin Users Receiving Antidepressant Treatment

3.1. Introduction

Type 2 diabetes significantly impacts the lives of people worldwide. As one of the most prevalent chronic diseases, it is associated with increased hospitalization rates, longer hospital stays and two-fold higher physician visits compared to those without diabetes; indeed, the burden of diabetes to society is an important consideration given that approximately half of individuals with diabetes are between the working ages of 25 and 64 years.(1-3) Unfortunately, the risk of depression is generally higher in these individuals as well(4); people with type 2 diabetes have a rate of depression two times higher than the general population.(5, 6)

Depression can be characterized as a remitting and recurring disease, with high rates of recurrence.(7) Depression is also a leading cause of disability worldwide, resulting in substantial functional impairment, increased costs to the healthcare system, and morbidity.(8-12) Individuals with depression often experience continued morbidity which can negatively impact self-directed management of chronic conditions. For example, type 2 diabetes requires good adherence to both healthy lifestyle interventions and antihyperglycemic medications to control blood glucose levels and prevent diabetes related complications.(13)

Although depression is a well-recognized risk factor for poor adherence to oral antihyperglycemic medications, the understanding of this relationship is very limited.(4, 14-18) The majority of studies examining the association between depression and adherence to oral antihyperglycemic medications are cross-sectional and utilize a static definition of prevalent depression.(19-21) In addition, there is a paucity of information regarding the effect of depression treatment on adherence to oral antihyperglycemic medications.(22-24) Given that

depression treatment has positive effects on diabetes self-care activities(24) it is possible that depression treatment may also improve adherence.

Treatment of depression is mainly non-pharmacological, pharmacological or a combination of both; all of which are proven to be effective.(25, 26) The Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines provide evidence-based recommendations for non-pharmacological treatments involving cognitive, behavioral, or supportive interventions and pharmacological intervention with antidepressant medications.(27) Given the fluidity of the disease, treatment remains individual-specific based on demographics, socioeconomic considerations, comorbidities, and disease severity.(27)

The main study objective was to explore the impact of depression treatment on adherence to oral antihyperglycemic drug therapy in individuals with diabetes and a new episode of depression. The aim was to characterize the non-pharmacologic and pharmacologic depression treatments recorded in administrative health data and define adherence to multidrug regimens. I hypothesized that individuals receiving treatment for depression would have better adherence to oral antihyperglycemic medications compared to those who did not receive treatment.

3.2. Participants and Methods

3.2.1 Population and setting

This population-based retrospective cohort study used administrative health data from Alberta, Canada between April 1, 2008 and March 31, 2018. Alberta Health's administrative databases are used to record health service utilization and reimburse healthcare providers under a universal healthcare system. The databases used for this study included the Population Registry, which contains demographic information; Ambulatory Care, which captures emergency department visits and day procedures; the Discharge Abstract Database, which contains

information on all hospitalizations; the Pharmaceutical Information Network, which has information on all prescription drug dispensations; and Practitioner Claims, which has information on all clinician service visits. The University of Alberta Health Research Ethics Board approved the study protocol (Pro00066037).

The sampling frame consisted of all Alberta residents dispensed at least one antihyperglycemic drug. Clinical practice guidelines recommend metformin as initial therapy in people with type 2 diabetes; therefore, the initiation of metformin served as a starting point for the study observation window.(28, 29) A standard new user definition was used to identify individuals initiating metformin therapy and to minimize the risk of including people with prevalent diabetes.(30) People were excluded if they were dispensed any antihyperglycemic drug or had less than 1 year of administrative health information prior to their first metformin dispensation record. Women using metformin as the only antihyperglycemic and having a health service claim for polycystic ovarian syndrome were excluded because it is unlikely that metformin was used to treat type 2 diabetes. People were also excluded if they were less than 18 years of age on the date of their first metformin dispensation.

New metformin users with depression were identified using a validated set of diagnostic codes.(31, 32)(Table 2.1) This set of codes has a positive predictive value of 92% to identify people with depression. The Practitioner Claims, Ambulatory Care, and Discharge Abstract Databases were searched for the earliest health service record for depression following metformin initiation. A new depression episode was defined as the first service record for depression occurring at least one year after initiating metformin therapy. The date of the service record served as the index date to define timepoints in the study.(Figure 3.1) People with less than 1 year between the index date and study exit date, and those receiving antidepressant

medications within the 6-month period before the index date were excluded.(Table 3.1) The minimum one-year interval between first metformin dispensation and first service record for depression, along with excluding prevalent antidepressant users, reduced the likelihood of including individuals with prevalent depression in the study.

3.2.2 Exposure assessment

Initially, four exposure groups were developed to specify if individuals received non-pharmacological treatment only, pharmacological treatment only, a combination of non-pharmacologic and pharmacologic treatment, or no treatment. This would have enabled an exploration of the impact of different treatment options on adherence. Non-pharmacological treatments could be identified using service codes for mental health counselling, cognitive behavioural therapy, or electroconvulsive therapy in the Practitioner Claims database.(Table 3.2) Pharmacological treatments could be identified from dispensation records in the Pharmaceutical Information Network database.(27, 33)(Table 3.1) However, when these treatment definitions were applied to the administrative databases, it was discovered that non-pharmacological treatment services were not recorded frequently. For example, many registered psychologists work in private practice settings and do not record counselling sessions with clients in provincial administrative databases. Given that psychological counselling is a recommended non-pharmacologic treatment for depression with strong evidence supporting its effectiveness, this was a significant and unexpected limitation encountered in operationalizing the exposure definitions.(24, 34)

Based on the observations, the exposure definition was restricted to those receiving pharmacologic treatment for the new depression episode. It was considered that an individual received pharmacologic treatment if there were at least 2 dispensation records for an

antidepressant within 90 days of the index date.(Figure 3.1) The 90-day exposure assessment window allowed time for initiating pharmacologic therapy and making adjustments in response to ineffective dosing or tolerability issues.(7, 27, 35)

3.2.3 Outcome measures

The outcome measure was adherence to multiple oral antihyperglycemic medications, defined as the proportion of days covered (PDC) during days 91-270 following the index date.(Figure 3.1) An algorithm was constructed to calculate the proportion of days that an individual had at least 1 of their antihyperglycemic medications available to them.(36, 37) First, days that had medication available were identified based on the dispense date and days of supply for each antihyperglycemic medication class. Second, this information was combined for each individual to identify the days that had at least 1 antihyperglycemic medication. For example, for an individual treated with metformin and a sulfonylurea, the day was considered covered if either or both medications were available.(Figure 2.2) Third, the duration of any hospitalizations were excluded from the numerator and denominator. Hospitalizations were treated as immeasurable time because the administrative health databases used in this study do not record inpatient drug use.(38) If an individual was hospitalized for >50% of the outcome assessment window, they were excluded because there was insufficient information to calculate a PDC. Last, the PDC was calculated by dividing the total number of days with drug available by the observation interval.

3.2.4 Covariables

Variables that may impact the association between depression and adherence were identified during the baseline period.(Figure 3.1) Sociodemographic information (age, sex, urban or rural residence) was determined on the index date. To adjust for concurrent medical

conditions, diagnostic codes were used from Practitioner Claims, Ambulatory Care, and Discharge Abstract Database to identify a predefined list of chronic conditions.(39, 40)(Table 2.2) In the analyses, the number of chronic conditions was used rather than binary indicators for each condition. Pre-existing diabetes-related complications and mental health conditions were identified using validated definitions where available and used binary indicators for each condition.(Table 2.2) Baseline haemoglobin A1c was the value closest to, but no more than 90 days from, the index date. Cardiovascular medications, and medications used for other chronic conditions were identified from dispensation records in the year before the index date.(Table 2.3) For the analyses, the number of cardiovascular and other medications were used rather than binary indicators for each drug. Last, the number of hospital admissions and practitioner claims were counted in the year before the index date. For the analyses, the hospital admissions count was collapsed to an ordinal variable with 3 categories: 0 visits, 1 visit, 2 or more visits. The practitioner claims count was collapsed to a dichotomous variable: 0 to 12 visits, 13 or more visits.

Depression severity is a composite of impairment, treatment, and recalcitrance, all of which may present differently in administrative data.(41) These patterns could be identified with ICD-9 and ICD-10 coding for mild (296.21, 296.31, F32.0, F33.0), moderate (296.22, 296.32, F32.1, F33.1), and severe (296.23, 296.24, 296.33, 296.34, F32.2, F32.3, F33.2, F33.3) depression. Initially, the aim was to use these codes to characterize depression severity and examine the association between depression treatment and drug adherence across a continuum of severity. Upon reviewing literature and corresponding with experts in this field, it was concluded that there are no validated methods to stratify depression based on severity using administrative data.(31) Most administrative data-based studies have focused on identifying depression itself

rather than adding the complexity of severity.(22-24) In addition, the data sources do not contain ICD-9 codes with 2 decimal places and ICD-10 codes with 4 digits. As a result, controlling for depression severity and how this may impact the results was not possible.

3.2.5 Statistical analyses

Baseline characteristics between exposure groups were compared using t-tests and chi square tests for continuous and categorical variables, respectively. Multivariable logistic regression modelling was used to determine if pharmacologic treatment of depression was independently associated with poor adherence. A PDC threshold of <80% was chosen to define poor adherence based on existing literature assessing oral antihyperglycemic drug adherence with claims databases.(42, 43) A multivariable model was constructed by first including all variables with reasonable univariate associations ($p<0.1$) with poor adherence. The model was refined by conducting backward elimination with a criterion of $p>0.1$ to remove a variable from the model. Collinearity was assessed using the variance inflation factor (VIF), with a value > 10 indicating variable refinement was required.(44) Once the multivariable model was defined, the adjusted odds ratio and 95% confidence interval were examined to identify factors that were independently associated with poor adherence. All analyses were conducted using Stata 16 (StataCorp LP, College Station, TX, USA).

3.2.6 Sensitivity Analyses

Five analyses were conducted to test the robustness of the findings by using alternate analytical models, alternate exposure definitions, and alternate outcome definitions. First, forward selection modelling was used to examine the effects of each covariable on the association between pharmacologic treatment of depression and poor adherence. Second, the length of the exposure assessment window was increased and considered a individual received

pharmacologic treatment if there were at least 2 dispensation records for an antidepressant within 180 days of the index date.(7) Third, the PDC threshold was increased to <90% to define poor adherence. The reasons for this were two-fold. Although the 80% threshold to define poor adherence is commonly used, some authors suggest higher thresholds are better predictors of health outcomes.(45, 46) As well, increasing the threshold may be reasonable because the algorithm considered the day covered if at least one drug was available, which would favour people using more than one antihyperglycemic medication. As an alternate approach to test the effect of the PDC algorithm on the observed results, the median PDC was used to define poor adherence in the fourth sensitivity analysis. In the last sensitivity analysis, baseline hemoglobin A1c was added to the multivariable models as a way to adjust for the severity of type 2 diabetes.

3.3 Results

As summarized in Figure 3.2, a total of 165,056 (77%) adult new metformin users were identified from 214,762 people dispensed an oral antihyperglycemic drug between April 1, 2008 and March 31, 2018. A total of 31,513 (19.1%) new metformin users had at least 1 depression-related service record after initiating metformin. Within this group, 7,220 (22.9%) had their first health service record for depression a minimum of one year after starting metformin, had at least 1 year before their study exit date, had no antidepressant dispensations in the previous 6 months and were not hospitalized for >50% of the outcome assessment window. The mean duration between metformin initiation and a new episode of depression was 3.0 (SD 1.6) years.

A total of 1,899 (26.3%) people received ≥2 dispensations for antidepressants within 90 days of the index date. A comparison of baseline characteristics between treatment groups is provided in Table 3.3. The mean age at index date was lower ($p<0.001$) and the proportion of women was higher ($p=0.012$) in the treated group compared to controls. Baseline hemoglobin

A1c was higher (p=0.027) for controls compared to the treated group.(Table 3.3)

3.3.1 Proportion of Days Covered in Year Prior to Depression

A large overlap in the distribution of PDC was observed between the treatment groups and the spread of data was clustered at PDC of 0 and 1.(Figure 3.3) The mean PDC was higher for the treated group (0.57 [SD 0.42]) compared to controls (0.55 [SD 0.43]); however, this difference was not statistically significant (p=0.13). When defining poor adherence as a PDC <0.8, there was a small, but non-significant difference in the proportions with poor adherence in the treated group (1,021, 53.8%) compared to controls (2,938, 55.2%) (p=0.28). After adjusting for other comorbidities and characteristics at baseline, pharmacologically treated depression was associated with a lower, but non-significant likelihood of poor adherence compared to no pharmacologic treatment (adjusted odds ratio 0.91; 95%CI 0.81,1.02).(Table 3.4)

3.3.2 Sensitivity Analyses

Forward selection modelling showed that pharmacologic treatment of depression was significantly associated with a lower likelihood of poor adherence after adjusting for differences in demographic variables, comorbidities, and health service visit frequencies.(Table 3.5) When adding cardiovascular and other chronic medications to the model, the association was no longer statistically significant. The mean number of cardiovascular and other chronic medications was significantly lower in those with poor adherence (2.6 [SD 2.2]) compared to those with good adherence (3.6 [SD 2.2]) (p<0.0001). When stratified by number of other medications, there was an apparent trend in the association with poor adherence. The proportion of individuals with poor adherence was highest in the group with few other medications and lowest in those with 6 or more medications.(Table 3.6)

Increasing the exposure assessment interval to 180 days and increasing the threshold for poor adherence to <90% produced results consistent to the main analysis.(Table 3.4) On the other hand, defining poor adherence using the median split of PDC at 0.67 produced an adjusted odds ratio similar in magnitude and direction but the association was statistically significant ($p<0.001$).(Table 3.4) Lastly, a total of 4,218 people had a baseline A1c value in the study group. A multivariable logistic regression model was conducted on this subgroup and observed an adjusted odds ratio that was similar in magnitude and direction to the main results.(Table 3.4)

3.4. Discussion

The goal of this study was to determine if treatment of a new episode of depression affected adherence to oral antihyperglycemic medications. Operationalizing the exposure definition, a significant revision had to be made by restricting to pharmacological treatment only. Provincial administrative databases do not contain comprehensive data on non-pharmacological treatments for depression since many clinicians providing these services do not submit claims to the publicly funded healthcare system. Individuals treated with antidepressants were 0.91 times less likely to have poor adherence; however, the association between treated depression and poor adherence was not statistically significant even after adjusting for other comorbidities and characteristics at baseline.

Examining the effects of depression treatment in individuals with diabetes is a developing area of research; as a result, there are a limited number of studies in the literature. Reviews done by Gonzalez and colleagues suggested a significant association between depression severity and self-care activities in individuals with diabetes.(19, 24) The results of these reviews indicated treatment of depression was effective in controlling depressive symptoms, and could have a positive influence on self-care activities to achieve glycemic control.(19, 24) Given this

association and considering depression as a well-recognized risk factor for poor adherence in diabetes(18-21, 23, 47-85), treatment of depression was expected to improve adherence to antihyperglycemic medications. Therefore, the study findings were surprising as the expected association was not seen between treated depression and adherence to oral antihyperglycemics.

Markowitz and colleagues had called for future studies to focus on the effects of depression treatment on adherence to treatments in individuals with type 2 diabetes.(24) Since that time, two studies have examined the association between depression treatment and either persistence(22) or adherence(23) to antihyperglycemic medications. In the first study, Caughey and colleagues identified antidepressant users based on dispensation records within the 6-month period before initiating antihyperglycemic medications.(22) They found that treated depression was associated with 1.4 times higher likelihood of discontinuing therapy (adjusted odds ratio 1.42; 95%CI 1.37-1.47). This observation differs in direction of the results found in this project by suggesting individuals receiving treatment for depression have poor management of oral antihyperglycemics compared to those who do not receive treatment. However, there are two important differences compared to this project to highlight. First, Caughey and colleagues used dispensation records to identify people with depression rather than diagnoses in clinician claims data. The control group was likely a heterogeneous mixture of people without depression and people with depression who were not currently receiving pharmacologic treatment. In contrast, this project identified a group of individuals with new depressive episodes and then compared those who were treated to those who were not treated. Second, Caughey and colleagues examined discontinuation of initial antihyperglycemic medications; median time to discontinuation was 1.81 years in people treated for depression and 3.23 years for controls. In

this study, I started following individuals after diagnosis of a new depressive episode, which occurred a mean of 3.0 years after initiating metformin therapy.

In the second study, Xing and colleagues used a claims-based definition to identify people using antipsychotics to manage a major depressive episode.(23) They found that the use of second-generation antipsychotics was associated with a 1.3 times higher odds of a ≥10% decline in adherence to oral antihyperglycemic medications (adjusted odds ratio 1.34; 95%CI 1.17-1.53). It is possible that antipsychotic medications may be an indicator for more severe depression and therefore introduced confounding by indication into this observed association. The variations in exposure and outcome exposure definitions, inconsistencies in results amongst these studies highlight the ongoing need to better understand how treatment of depression can affect antihyperglycemic use.

To explore factors influencing the observed association, forward selection modelling was used to identify possible sources of confounding. Adding the number of cardiovascular medications and medications for other chronic conditions to the model negated the significant association first seen between treated depression and poor adherence.(Table 3.5) Further exploration of the number of cardiovascular and other medications revealed some unexpected results. When this variable was transformed into an ordinal variable, individuals with few other medications had the highest proportion of poor adherence and those with 6 or more medications had the lowest proportion of poor adherence.(Table 3.6) This finding is counter-intuitive as pill burden (the number of different chronic medications a person is using) is considered a risk factor for poor adherence.(86, 87) However, in the context of depression management, the opposite has been seen.(23) Higher pill burden can be an indicator for more utilization of clinician services, including more frequent follow-up and monitoring between a clinician and an individual with

depression. In fact, when stratified by number of clinician visits, the proportion of individuals with poor adherence was highest in the group with few clinician visits. The analysis aligned with the idea that there is a trend of higher number of clinician visits and lower likelihood of poor adherence.(Table 3.4)

As with forward selection modelling, the use of exploratory data analysis identified other limitations of the data. A histogram of PDC values showed substantial overlap between those treated for depression and those who did not receive treatment.(Figure 3.3) The overlap could contribute to difficulty in observing a difference between the two groups. As one solution to address this issue, poor adherence was defined using the median PDC. This median split approach produced adjusted odds ratios that were not only similar in magnitude and direction, but also showed a statistically significant association between depression treatment and adherence ($p<0.001$).(Table 3.4)

The study contributes to limited existing literature on the relationship between treated depression and medication adherence to oral antihyperglycemic medications. First, study groups were defined based on the diagnosis of a new depressive episode. Unlike previous studies, this study reduced the likelihood of including people with prevalent depression and established a reasonably homogeneous control group.(22) Second, pharmacologic treatment was defined using antidepressants recommended by CANMAT and WHO guidelines for treatment of a depressive episode.(27) Third, the use of calculating PDC to multiple oral antihyperglycemics accounted for the dynamic medication regimens that individuals with diabetes often have that cannot be captured by simply calculating PDC to a single oral antihyperglycemic medication.

To my knowledge, this is the first study to measure adherence to oral antihyperglycemic medications following antidepressant treatment for a new episode of depression in a cohort of

individuals with type 2 diabetes. Previous studies have highlighted the negative impact of depression on adherence to oral antihyperglycemics; however, it remained unknown if depression was in fact a risk factor that could be modified by appropriate treatment.(19) Continuous diabetes medication management strategies are required to achieve disease control and optimal health outcomes.(1) It is important to consider that depression affects more than just an individual's mood and can influence physical functioning, including medication taking behaviours.(88) The study findings may encourage clinicians to identify individuals with type 2 diabetes who may be at risk of poor adherence to antihyperglycemics and develop appropriate treatment plans for both diabetes and depression care. Appropriate interventions for episodes of depression may help improve adherence, consequently preventing adverse health outcomes.

Important strengths of this study are the use of standardized definitions of depression and antidepressant treatment using claims data to assess concurrent adherence to multiple medications.(37) The use of a 6-month washout period of no antidepressant dispensations prior to a new depressive episode reduced the risk of including individuals with prevalent depression. Another strength of this study design was examining adherence for those initiated on metformin and allowing for those who switched or added on other antihyperglycemics by using the "at least one" definition. Generally, studies have focused on adherence to a single medication and whereas this study addressed a broader clinical image as part of chronic management. Using the "at least one" definition when calculating PDC by multiple medications allowed for an individual to be considered adherent regardless if they discontinued one of their medications and were adherent to the other. As well, considering multiple antihyperglycemic medications and having a large cohort of individuals using claims data contributes to the results being more generalizable.

There are also several important limitations to consider when interpreting the observations seen. First, there are methodological issues of using administrative data to define non-pharmacological treatment given administrative data is primarily used for billing purposes and clinicians providing these services, such as psychotherapy, are often privatized. Therefore, it could not be determined if a control not treated with antidepressants were in fact receiving non-pharmacological treatment for depression; this may have reduced the difference in effect seen. Second, it was not possible to determine the impact of depression severity on adherence. Third, a major assumption made was individuals filling their prescriptions aligned with them actually taking their medications. Fourth, the results of pill burden showing better adherence could have been associated to automatic fills by pharmacies or patients on adherence aids who many not necessarily be taking their medications but receiving new supplies or may be receiving help through the use of adherence aids to maintain adherence. Fifth, antidepressants can be used for indications other than depression; for example, tricyclic antidepressants can be used for anxiety and neuropathic pain management. People using antidepressants for indications other than depression would have been excluded, possibly introducing selection bias. This is likely a minimal issue as the prevalence of anxiety and neuropathies was similar between the two groups and these factors were included in the multivariable analyses.(Table 3.3) Lastly, the study individuals included new metformin users instead of new antihyperglycemics users. From other studies, it is known that not all individuals with diabetes initiate pharmacological therapy with metformin(22); therefore, the definition was less inclusive and did not capture those individuals who were initiated on oral antihyperglycemics other than metformin. However, only 11,714 (5.4%) out of 214,762 people were started on other antihyperglycemics instead of metformin and represented a very small minority of the population in our dataset.

3.5. Conclusion

Individuals with newly diagnosed type 2 diabetes and a new episode of depression appeared to be less likely to have poor adherence to oral antihyperglycemic medications following treatment with antidepressants. While statistical significance was not achieved, it is plausible that the difference in adherence between the two groups was masked by a major confounding effect related to number of other medications used. The clinical significance of this association warrants further research. For clinicians treating individuals with type 2 diabetes and comorbid depression, appropriate interventions for depressive episodes may improve adherence to antihyperglycemic medications. Future studies should examine the impact of non-pharmacological treatment interventions for depression on adherence to oral antihyperglycemic medications.

3.6. References

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Table 3.1. Anatomical Therapeutic Chemical (ATC) Codes Used to Identify Antidepressants.

Antidepressant (Brand Name(s))	Anatomical Therapeutic Chemical (ATC) Code
First Line	
Agomelatine (Valdoxan)	N06AX22
Bupropion (Wellbutrin)	N06AX12, A08AA62
Citalopram (Celexa, Cipramil)	N06AB04
Desvenlafaxine (Pristiq)	N06AX23
Duloxetine (Cymbalta)	N06AX21
Escitalopram (Cipralex, Lexapro)	N06AB10
Fluoxetine (Prozac)	N06AB03, N06CA03
Fluvoxamine (Luvox)	N06AB08
Mianserin (Tolvon)	N06AX03
Milnacipran (Ixel)	N06AX17
Mirtazapine (Remeron)	N06AX11
Paroxetine (Paxil)	N06AB05
Sertraline (Zoloft)	N06AB06
Venlafaxine (Effexor)	N06AX16
Vortioxetine (Brintellix, Trintellix)	N06AX26
Second Line	
Amitriptyline, clomipramine, and others	N06AAxx
Moclobemide (Manerix)	N06AG02
Quetiapine (Seroquel)	N05AH04
Selegiline transdermal (Emsam)	N04BD01
Trazodone (Desyrel)	N06AX05
Vilazodone (Viibryd)	N06AX24
Third Line	
Phenelezine (Nardil)	N06AF03
Tranylcypromine (Parnate)	N06AF04
Reboxetine (Edronax)	N06AX18
Tryptophan†	N06AX02

*Antidepressants as recommended by CANMAT treatment guidelines and listed in Table 3.(27)
†WHO list of agents to treat depression(33)

Table 3.2. Service Codes Used to Identify Non-Pharmacological Treatment of Depression.

Alberta Medical Association Service Codes*	
08.11A	Requiring complete mental status examination and investigation
08.11B	Evidence from a psychiatrist at a Review Panel on behalf of a specific patient
08.11C	For complex patient, requiring complete mental status examination and investigation
08.19A	Formal major psychiatric consultation
08.19AA	Formal major psychiatric consultation for a patient referred by a registered: occupational therapist, psychologist, community based psychiatric nurse, social worker or speech language pathologist
08.19B	Minor psychiatric consultation
08.19BB	Minor psychiatric consultation for a patient referred by a registered: occupational therapist, psychologist, community based psychiatric nurse, social worker or speech language pathologist
08.19C	Repeat psychiatric consultation
08.19CC	Repeat psychiatric consultation for a patient referred by a registered: occupational therapist, psychologist, community based psychiatric nurse, social worker or speech language pathologist
08.19D	Professional interview with relative(s) in connection with the management of a patient with a psychiatric disorder
08.19F	Formal, scheduled, professional conference related to the care and treatment of a psychiatric patient with other physician(s), and/or direct therapeutic supervision of, allied health professionals, educational, correctional and other community agencies on behalf of a specific patient
08.19G	Direct contact with an individual patient for psychiatric treatment (including medical psychotherapy and medication prescription), psychiatric reassessment, patient education and/or general psychiatric counselling
08.19GA	Direct contact with a patient for psychiatric treatment, psychiatric reassessment, patient education and/or psychiatric counseling
08.19GB	Direct contact with a complex patient for psychiatric treatment (including medical psychotherapy and medication prescription), psychiatric reassessment, patient education and/or psychiatric counseling
08.19H	Second and subsequent physician attendance at a formal, scheduled, professional conference related to the care and treatment of a psychiatric patient, on behalf of a specific patient
08.19J	Formal, scheduled, professional conference related to the care and treatment of multiple psychiatric patients with other physician(s), educational, correctional and other community agencies on behalf of a specific patient

08.19K	Second and subsequent physician attendance at a formal, scheduled, professional conference related to the care and treatment of multiple psychiatric patients
08.19M	Second physician involved in the issuance, development and documentation of a CTO
08.19N	Renewal, amendments, cancellation or expiry of a CTO as well as necessary work involved in the completion of an apprehension order, examination on apprehension, written statement or non-compliance report
Therapeutic Interventions for Mental Health Canadian Classification of Mental Health Interventions Codes*	
6.AA.10.BE	Counselling for behavior
6.AA.10.MA	Counselling for mood
6.AA.10.ZZ	Counselling for other reasons
6.AA.30.BE-AA	Active listening for behavior
6.AA.30.MA-AA	Active listening for mood
6.AA.30.MA-PA	Light therapy for mood
6.AA.30.MA-RA	Music therapy for mood
6.DA.10.D	Interpersonal relationships
The Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures Codes*	
8.38	Electroconvulsive therapy

*Retrieved from Alberta Medical Association Fee Navigator(89)

Table 3.3. Baseline Characteristics.

Characteristic*	Active Depression Episode Group n= 1,899	Control Group n= 5,321	p-Value
Demographics			
Age, years†	54.8 (±15.7)	56.6 (±15.4)	<0.001
Men, n(%)	850 (44.8)	2,560 (48.1)	0.012
Urban Residence, n(%)	1,576 (83.0)	4,555 (85.6)	0.006
Metformin Duration, years†	3.0 (±1.6)	3.0 (±1.6)	0.54
Baseline HbA1c %†	7.2(±1.7)	7.3(±1.7)	0.027
Number of Medications Claimed Other than OAH†	3.21 (±2.3)	3.01 (±2.2)	<0.001
Number of Medications Claimed Other than OAH, n(%)			0.019
0-1	1,561 (29.0)	498 (26.1)	
2-3	1,794 (33.3)	620 (32.4)	
4-5	1,221 (22.7)	474 (24.8)	
≥ 6	809 (15.0)	319 (16.7)	
Number of Comorbidities†,‡	5.7 (±2.8)	5.9 (±2.7)	0.001
Mental Health Disease			
Anxiety Disorders, n(%)	564 (29.7)	1,516 (28.5)	0.32
Bipolar, n(%)	24 (1.3)	138 (2.6)	0.001
Brain Diseases (Alzheimer's, Dementias), n(%)	142 (7.5)	467 (8.8)	0.08
Diabetes Complications			

Renal, n(%)	333 (17.5)	925 (17.4)	0.88
Neuropathy, n(%)	267 (14.1)	737 (13.9)	0.82
Amputations, n(%)	41 (2.2)	135 (2.5)	0.36
Diabetic Foot Infections, (n%)	194 (10.2) 214 (11.2)	541 (10.2) 675 (12.5)	0.95
Ophthalmic, n(%)	262 (13.8)	799 (15.0)	0.20
Hypoglycemia, n(%)	61 (3.2)	163 (3.1)	0.75
Dental, n(%)	166 (8.7)	506 (9.5)	0.32
Number of Clinician Visits, n(%)			0.082
0	21 (1.1)	51 (1.0)	
1-12	695 (36.6)	1,909 (35.9)	
13-24	512 (27.0)	1,475 (27.7)	
25-36	270 (14.2)	800 (15.0)	
37-48	150 (7.9)	426 (8.0)	
≥49	251 (13.2)	660 (12.4)	
Number of Hospitalizations, n(%)			0.013
0	1,501 (79.04)	4,363 (82.0)	
1-2	285 (15.0)	707 (13.3)	
≥ 3	113 (6.0)	251 (4.7)	

OAH= Oral Antihyperglycemic Medications
*Values reported as count and percentage
†Values reported as mean and (standard deviation)
‡Chronic conditions as listed by Elixhauser et al.(40)

Table 3.4. Multivariate Logistic Regression Models Examining Association Between Active Depression Treatment and Poor Adherence.

	Main Analysis† (N=7,220)	**Main analysis with length of exposure assessment window extended to 180 days from index† (N=7,220)**	**Main analysis with poor adherence threshold <90%† (N=7,220)**	**Main analysis with subgroup of individuals that have A1c at baseline (N=4, 153)**	**Main analysis with poor adherence defined at the median PDC (N=7,220)**
Treated Depression	0.91 (0.81, 1.02)	0.92 (0.83, 1.02)	0.94 (0.84, 1.05)	0.90 (0.78, 1.04)	0.86 (0.77, 0.96)
Age	0.97 (0.97-0.98)	0.98 (0.97-0.98)	0.97 (0.97-0.98)	0.98 (0.98-0.99)	0.97 (0.97-0.98)
Men	0.64 (0.58-0.71)	0.65 (0.59-0.71)	0.66 (0.60-0.73)	0.74 (0.65-0.84)	0.63 (0.57-0.69)
Number of chronic comorbidities‡	1.04 (1.02-1.06)	1.03 (1.00--1.05)	1.04 (1.02-1.06)	1.06 (1.03-1.09)	1.04 (1.01-1.06)
Baseline A1c	Not included	Not included	Not included	0.92 (0.88-0.95)	Not included
Anxiety	1.27 (1.13-1.42)	1.16 (1.04-1.30)	1.30 (1.16-1.46)	1.32 (1.15-1.53)	1.20 (1.07-1.34)
Cerebral	1.58 (1.31, 1.91)	1.47 (1.22-1.77)	1.38 (1.15-1.67)	1.66 (1.31-2.11)	1.69 (1.40-2.04)
Number of clinician visits	0.83 (0.74-0.93)	0.83 (0.74-0.93)	0.89 (0.79-1.00)	0.85 (0.73-0.99)	0.85 (0.76-0.96)
Number of hospitalizations 1 2	 1.59 (1.37-1.86) 2.52 (1.96-3.24)	 1.59 (1.37-1.86) 2.23 (1.75-2.84)	 1.36 (1.17-1.59) 1.98 (1.55-2.54)	 1.46 (1.20-1.78) 2.22 (1.64-3.02)	 1.66 (1.42-1.93) 2.54 (1.99-3.25)
Number of medications other than OAH	0.83 (0.81-0.85)	0.85 (0.83-0.87)	0.85 (0.83-0.87)	0.86 (0.83-0.89)	0.84 (0.81-0.86)
Metformin Duration	0.95 (0.93-0.98)	0.95 (0.92-0.98)	0.95 (0.93-0.98)	0.97 (0.93-1.00)	0.97 (0.94-1.00)

*All Odds Ratios and 95% Confidence Intervals are adjusted for the other variables in the table

†Model created by including all variables with P <0.1 in univariate analysis(Table 3.3), then performing backward elimination with a significance level of P > 0.1 to eliminate variables.
‡Chronic conditions as listed by Elixhauser et al.(40)

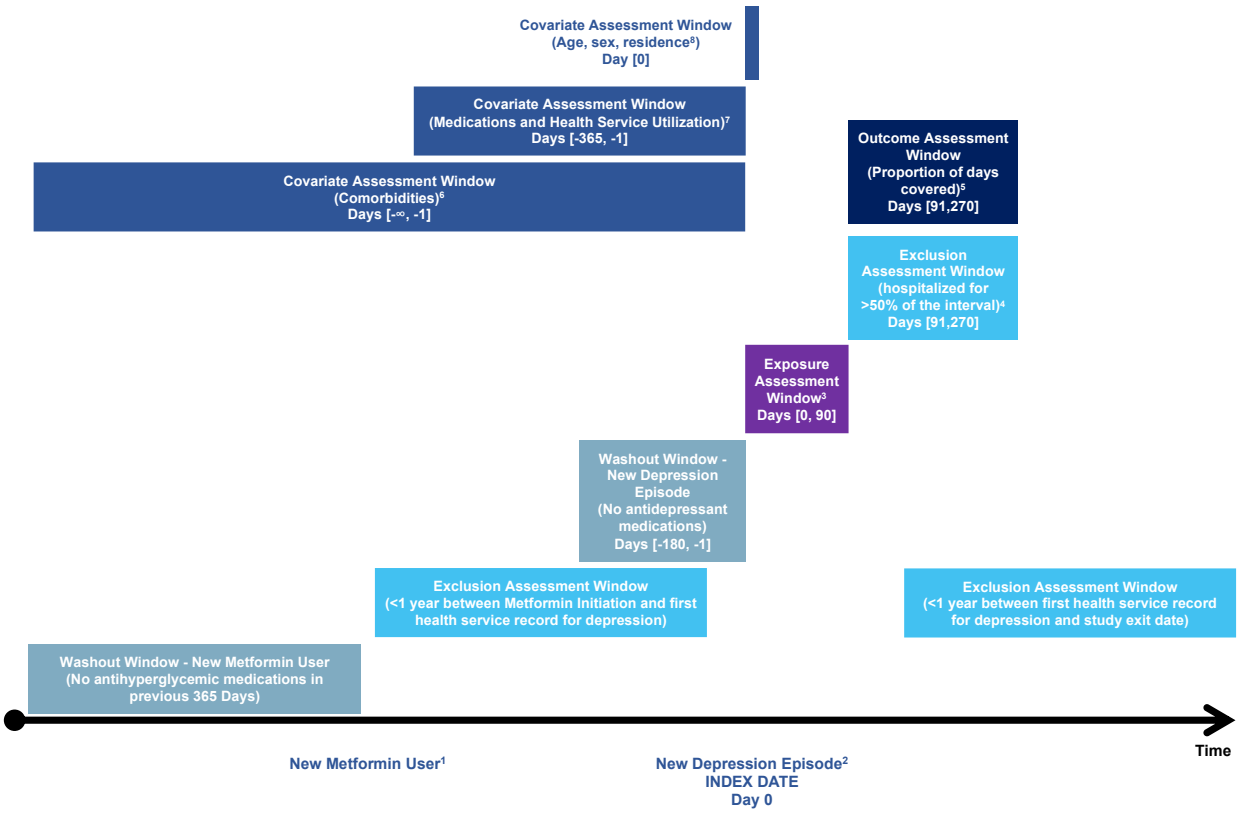
Table 3.5. Forward Selection Modelling of Multiple Logistic Regression to Examine Association Between Depression Treatment and Poor Adherence.

Variables in adjusted analysis	Odds ratio of treated depression group (95% CI)
None	0.94 (0.85, 1.05)
Age, sex	0.88 (0.78, 0.98)
Age, sex, duration of metformin	0.88 (0.78, 0.98)
Age, sex, duration of metformin, Elixhauser comorbidities(40)	0.88 (0.79, 0.98)
Age, sex, duration of metformin, Elixhauser comorbidities(40), anxiety, cerebral	0.88 (0.78, 0.98)
Age, sex, duration of metformin, Elixhauser comorbidities(40), anxiety, brain diseases (Alzheimer's, Dementias)	0.88 (0.78, 0.98)
Age, sex, duration of metformin, Elixhauser comorbidities(40), anxiety, brain diseases (Alzheimer's, Dementias), clinician visits, hospitalizations	0.86 (0.77, 0.96)
Age, sex, duration of metformin, Elixhauser comorbidities(40), anxiety, brain diseases (Alzheimer's, Dementias), clinician visits, hospitalizations, cardiovascular medications, other medications for chronic conditions	0.91 (0.81, 1.02)

Table 3.6. Proportion of Individuals with and without Poor Adherence According to Categories of Cardiovascular Medications and Other Prescription Medications

Number cardiovascular medications and other medications for chronic conditions	Individuals without Poor Adherence	Individuals with Poor Adherence
0-1	583 (28.6%)	1,458 (71.4%)
2-3	1,114 (46.6%)	1,278 (53.4%)
4-5	890 (53.1%)	787 (46.9%)
6 or more	674 (60.7%)	436 (39.3%)

Figure 3.1. Visual Representation of the Study Design.



1. Individual considered a New Metformin User based on a minimum of 1 year as a registered beneficiary in Alberta Health, no antihyperglycemic medications (including insulin) dispensed within 1 year before first metformin dispensation, age ≥18 years on date of first metformin dispensation and no history of Polycystic Ovarian Syndrome diagnoses.
2. Date of first health service record (Practitioner Claim, Ambulatory Care Service, or Hospitalization) for depression [See Table 2.1 for codes] that is ≥1 year after first metformin dispensation, ≥1 year before the study exit date for the individual, and the individual is not currently using antidepressant medications [See Table 3.1 for codes].
3. Exposure group assignment based on dispensation records in the Pharmaceutical Information Network database. Treated Group: ≥1 dispensation record for an antidepressant medication recommended by CANMAT or the WHO [See Table 3.1 for codes]. Control Group: <2 dispensation records for an antidepressant medication.
4. Time spent in hospital considered immeasurable time(38) because Alberta Health does not record in-hospital medication use. Individual excluded if they were admitted to a hospital for >50% of the interval used to calculate proportion of days covered.

5. Proportion of days covered calculated for multiple oral antihyperglycemic medications (See Figure 2.2).
6. Comorbidities included a predefined list of chronic conditions(40), cardiovascular disease, and diabetes-related comorbidities [See Table 2.2 for complete list of comorbidities and codes]. Health service records (Practitioner Claims, Ambulator Care Service records, and Hospital separations) were reviewed from April 1 of the study individual's enrolment year as a registered beneficiary in Alberta Health until the Index Date.
7. Cardiovascular medications, antihyperglycemic medications (excluding metformin), and other chronic mediations [See Table 2.3 for complete list and codes]. Pharmaceutical Information Network dispensation records were reviewed for the 1-year period prior to the Index Date.
8. Place of residence was defined as urban or rural based on the Canada Post forward sortation area coding.

Figure 3.2. Study Individual Flow Diagram.

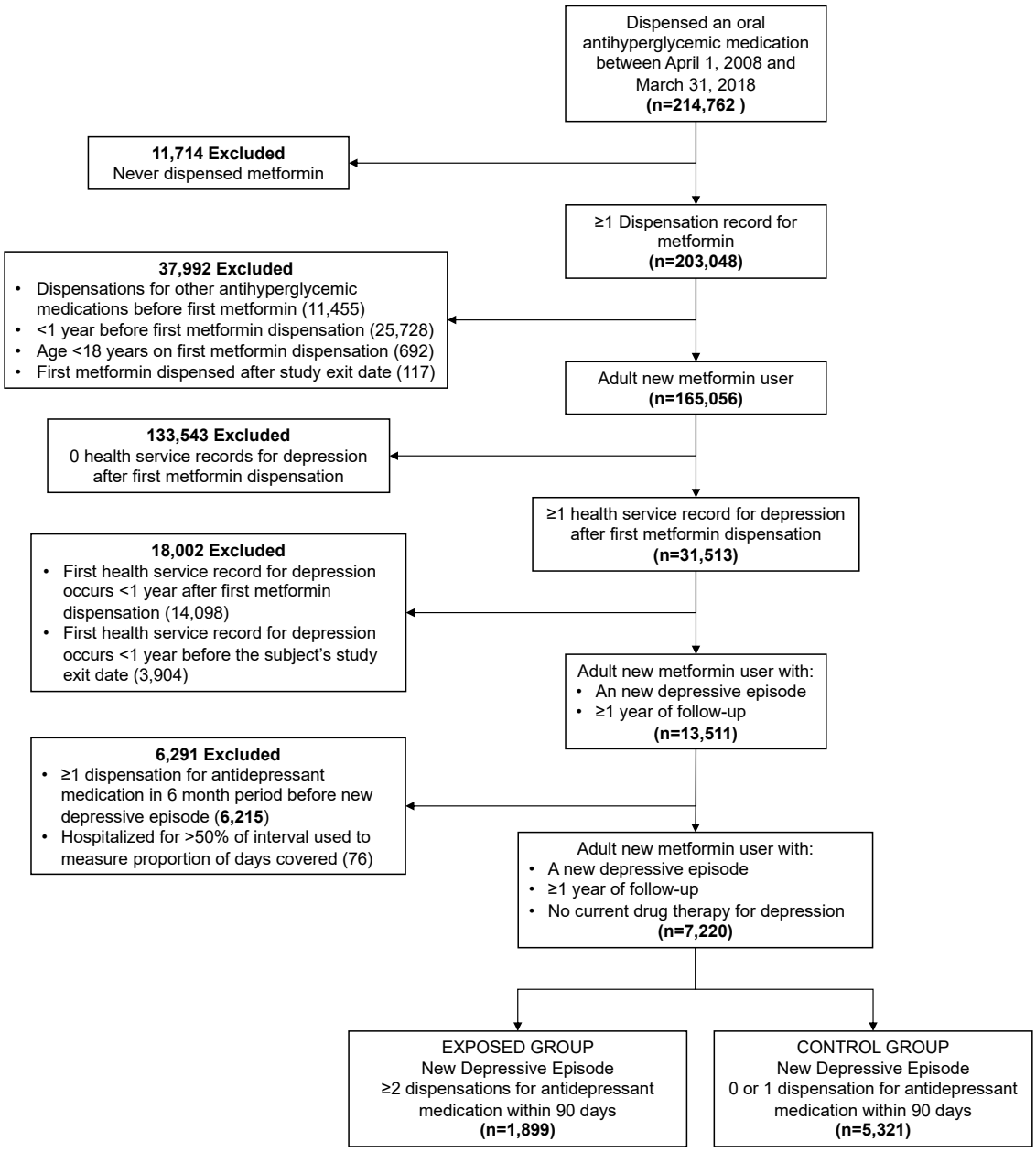
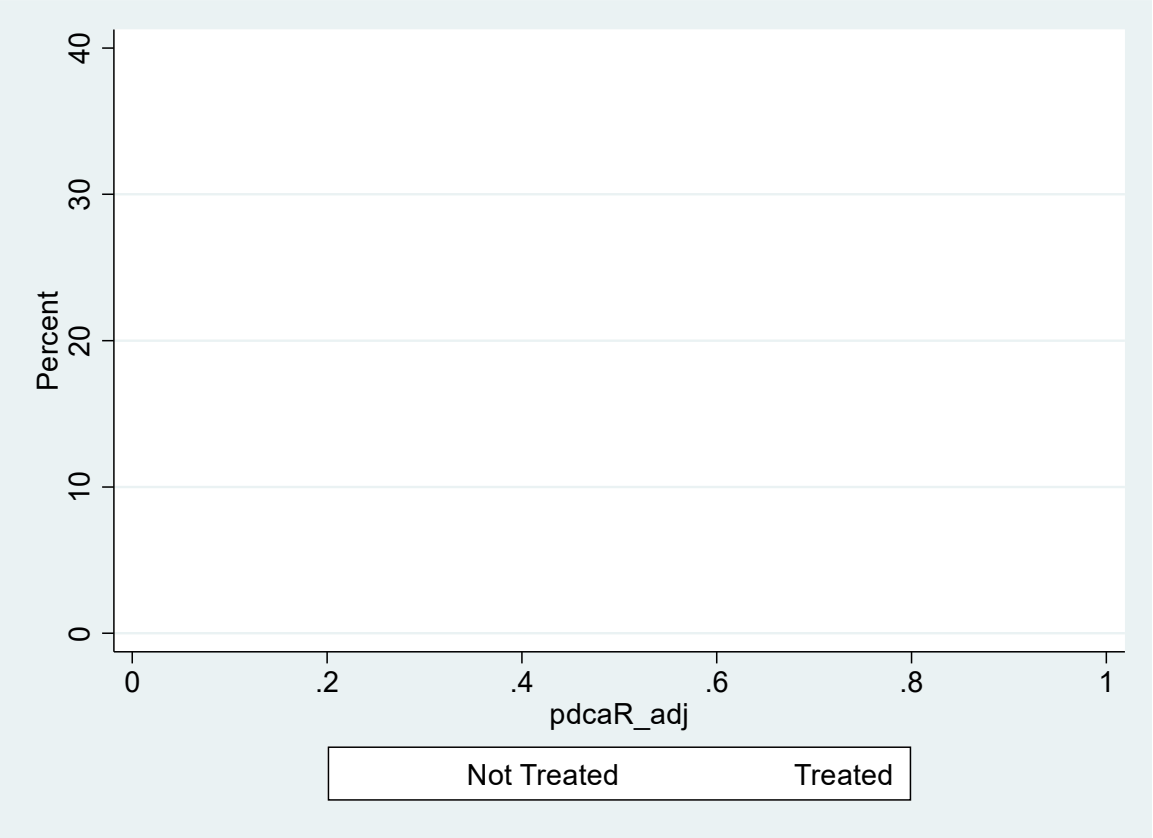


Figure 3.3. Histogram of proportion of days covered by treatment and no treatment groups.



CHAPTER 4: Summary, Conclusions and Implications

4.1 General Summary

Depression is often documented in the diabetes literature as a risk factor for poor adherence(1-45); however, there are many unknown details surrounding this association. For example, its association with adherence prior to an established diagnosis of depression is not documented. This is concerning, especially because symptoms of depression can be present well before the individual seeks medical care and primary care physicians only recognize depression in approximately half of their depressed patients.(46) Even after depression is diagnosed, the effect of treatment on adherence is not well described.(19) The overall aim of this thesis was to close these gaps in the literature by examining adherence to oral antihyperglycemics in the year preceding a diagnosis of comorbid depression and by examining the effect of depression treatment on adherence.

A vast majority of studies in the diabetes literature reporting the association between depression and adherence are cross-sectional surveys.(3, 5-8, 10, 12, 14, 17, 18, 20-25, 27, 30-33, 35-42, 45) These studies used self-reported scales like the Patient Health Questionnaire to identify people with depression and the 4-item scale developed by Morisky to measure adherence.(33, 36) The remaining studies were cohort studies that measured adherence after depression was identified, mainly from patient self-report.(1, 2, 4, 9, 11, 13, 15, 16, 19, 26, 28, 29, 34, 43, 44) The projects in my thesis used a validated case definition to identify people with a new depressive episode from International Classification of Disease codes.(47) The first project (Chapter 2) measured adherence in the year prior to depression diagnosis using a traditional proportion of days covered method as well as group based trajectory modelling. The second

project (Chapter 3) measured adherence following pharmacologic treatment of a new depressive episode.

The next 2 sections will explain the decision-making process that occurred while developing the methodology for both projects.

4.1.1 Summary of Chapter 2

The exposure group consisted of individuals with a new episode of depression. My initial plan was to establish an ordinal exposure variable using ICD coding that reported levels of depression severity so that disease severity could be considered in exploring adherence. Many decisions needed to be made including whether to focus on the first diagnostic code for a patient, what to do if the code indicated pre-existing depression (e.g., remission or a recurrent episode), if multiple codes were considered then what to do if the code changed (e.g., started at mild, then the next code indicated moderate). To help answer these questions, I reached out to authors of a paper reviewing validated depression case definitions using administrative data.(47) Specifically, I sought guidance regarding resources or validated methods to come to these decisions and how to stratify depression severity in administrative data beyond simply identifying depression itself. While I confirmed the importance of using validated case definitions for depression, unfortunately, Alberta Health data does not contain five-digit ICD-9 and four-digit ICD-10 coding that would distinguish between mild, moderate and severe depression. Therefore, I was unable to characterize depression severity in the exposure variable. My focus then shifted to identifying the most appropriate codes to identify depression by searching the literature, cross-checking ICD-9/10 chapters for coding, and looking into the data to assess whether such coding was available. This process was repeated for identifying the comorbidities used in all multivariable analyses.

A one-year washout period was used to rule out prevalent depression in the exposed group; if a person did not have a service record for depression in the last year, it is unlikely that they are experiencing an active depressive episode.(48) The variable and unknown duration of a prevalent depressive episode could bias the observed adherence rates. This concern is consistent with Feinstein's point that "each member of a cohort must have a chronologic reference point."(49) The one-year washout also gave assurance that each member in the group with depression was identified at the same point in the evolution of this condition. Furthermore, the interest was in examining the period of time leading up to a depression diagnosis and the one-year provided enough time to assess whether symptoms of depression impact on oral antihyperglycemic use.(48) Lastly, the one-year washout also ensured there was a sufficient period of time to calculate PDC for oral antihyperglycemic medications.(50)

The control group consisted of those who did not have any ICD codes for depression. The control group individuals were assigned depression diagnosis dates from the exposure group to minimize the risk of immortal time bias. Suissa describes this form of selection bias occurs when an exposure definition in a cohort study is defined in such a way that the outcome of interest cannot occur.(51) In Chapter 2, individuals in the control group may have been captured at various time periods of their diabetes management; the variable and unknown duration of diabetes could bias the observed adherence rates. To mitigate this bias, depression diagnosis-time matching was used; this approach was consistent with method 4 (prescription time-distribution matching) proposed by Zhou and colleagues for addressing immortal time bias.(52) For each person without depression, a time between metformin initiation and depression diagnosis was randomly selected from those with depression. Similar duration of diabetes accounts for extraneous factors that may affect adherence rates among the depression and control groups.

Extraneous factors can range from different levels of disease severity, experience managing disease or beliefs and perceptions of the disease. This aligned with methodology reported by Lunghi and colleagues to ensure people had a similar duration of diabetes to avoid immortal time bias.(29)

To examine the outcome variable, a Stata algorithm was used to develop the PDC calculations to work within the dataset, address overlapping fills, and measure adherence to multiple medications. Within this process, de novo code was created and cross validated with previous work by Linden.(53) The de novo code calculated the proportion of days that an individual had at least 1 of their antihyperglycemic medications available to them.(50, 54) Adherence was initially measured and reported using PDC for metformin only because clinical guidelines recommend metformin as initial therapy and my sampling frame was new metformin users.(55) As well, 60% of all antihyperglycemic dispensation records within our dataset were for metformin. Since side effects to metformin are manageable by appropriate initiation and titration, few people discontinue or switch off metformin.(82) However, some people may use antihyperglycemic medication regimens that exclude metformin, therefore I chose to re-calculate the PDC was re-calculated using all antihyperglycemic medications rather than focusing on metformin only. Although this predictably increased the observed PDC (mean 0.59 for metformin alone versus 0.63 when considering all antihyperglycemic medications), there were no changes to the magnitude, direction, or statistical significance of any of the results. Chapter 2 was revised to incorporate this change in PDC calculation.

The analysis was taken one step further by exploring trajectories of adherence. A review of previous studies using this medium for illustrating medication adherence influenced my decision to examination its usefulness for testing my hypothesis. Following the work of lead

authors in this field(57, 58), similar methods were used to approaching such analyses. Trajectory methods used paralleled Nitesh Choudhry and colleagues' while incorporating Nagin's principles to determine the best fitting model to the data.(59)

Following Nagin's guidelines to modelling, the initial model began with two trajectories and the number of trajectories increased consecutively to assess the best fit for the data.(59) Using Bayesian Information Criterion (BIC), lowest value as target, observations showed as the number of groups increased, BIC also increased. Therefore, the BIC was useful in identifying the shapes of trajectories and was not used to identify the number of trajectories. For the number of trajectories, the principle of parsimony was used. This principle involves developing the simplest model; therefore, it was settled to achieve a balance between the number of unique trajectories and maintaining group sizes of at least 5% of the overall sample in each group.(59) After selecting the number of groups, various orders of the polynomials were used to describe shapes of the trajectories.

Calculating a PDC within 30-day windows did present additional challenges when considering hospitalizations. Hospitalizations were considered immeasurable time; the duration of any hospitalization was removed from the numerator and denominator.(83) Within this process, the algorithm calculating a 30-day PDC would return a missing variable if the individual was hospitalized for >15 days. To replace missing data, a variety of methods were considered including random selection, carrying forward previous values, trimming missing values or mean imputation. Mean imputation was selected and an individual's mean 30-day PDC for all available windows was imputed into the windows with missing data. This approach was consistent with method 3 (individual mean) proposed by Shrive and colleagues addressing missing data.(60)

Lo-Ciganic's paper on adherence trajectories and hospitalizations inspired re-evaluation of the exposure and outcome variables.(61) In Lo-Ciganic's paper, the exposure variable is adherence to oral antihyperglycemic medications, and the outcome is the risk of hospitalizations. In Chapter 2, the x and y variables seemed to be opposite of what is often found in literature on trajectories. Therefore, I created an excel document of five trajectory articles that had consistent methodology.(57, 58, 62-64) The methods in Chapter 2 aligned with those in the reviewed articles and only differed by the outcome being studied. While it could have been possible to explore the risk of developing depression using trajectories, it was decided to maintain parsimony in the analysis and stick to the initial objective of measuring the outcome of adherence and using trajectories as an addition to the analysis.

Initially, the expectation of utilizing the trajectories approach was that there would be a definitive pattern of adherence (e.g., a sudden drop in the PDC) in the months before depression was recorded in the administrative data in the exposed group. Unfortunately, a clear pattern was not found that distinguished between people with and without depressive symptoms. However, it is important to report these neutral results to inform other researchers of limitations with this method. With these issues in mind, the association between depression and poor adherence was elected to be identified from the trajectory results. Poor adherence was defined using trajectories 1-4 and its association was examined with depression.

4.1.2 Summary of Chapter 3

Poor adherence is a complex phenomenon that can be caused by illnesses, socioeconomic factors, or experiences within the health care system.(65) Chapter 2 established that poor adherence to oral antihyperglycemics is present prior to a diagnosis of depression in individuals with type 2 diabetes; however, this led to the question of how treatment of the depressive episode

might affect adherence. Chapter 3 explored whether treating depression would improve adherence to antihyperglycemics medications in individuals with a new depressive episode compared to controls.

Chapter 3 sought to examine how different treatment options for depression impacted adherence to antihyperglycemic medications. Initially, the exposure was defined by four groups: individuals who received non-pharmacological treatment only, pharmacological treatment only, a combination of non-pharmacologic and pharmacologic treatment, or no treatment. However, a major limitation of the administrative databases was discovered regarding lack of information on non-pharmacological treatment services. Registered psychologists work in private practice settings and do not record services, including cognitive behavioral therapy, behavioral activation or interpersonal therapy, with clients in provincial administrative databases. Given that these services are a recommended non-pharmacologic treatment for depression with strong evidence supporting their effectiveness, this was a significant and unexpected limitation encountered in operationalizing the exposure definitions.(66, 67)

To better operationalize the exposure definition using the data available, the exposure definition was restricted to those receiving pharmacologic treatment for the new depressive episode.

The duration of the exposure assessment window involved contemplating an appropriate amount of time to allow for initiation of pharmacologic therapy. A 90-day duration was chosen as it surpassed the recommended minimum 4-8 weeks of treatment initiation required to assess whether an individual on an antidepressant is not responsive, partially or fully responsive to treatment.(48, 68, 69) One of the strategies to address no response or partial response to antidepressant treatment is to assess side effects and interactions with other concurrent

medications.(69) Therefore, the 90 days allowed enough time to initiate pharmacologic therapy, conduct an assessment of safety and effectiveness after a sufficient amount of time had passed of being on therapy, then make adjustments as needed.(48, 68, 69) For example, if an individual did not tolerate an initial antidepressant after 2-4 weeks, they would require up to an additional 8 weeks to assess full response to the new antidepressant selected. It is not uncommon to trial more than one antidepressant before finding the most appropriate medication for an individual(69, 70) and I wanted to capture enough time to allow for this. As well, a sensitivity analysis was conducted increasing the length of the exposure assessment window to 180 days of the new depressive episode date producing similar results to using the 90 days window.

The outcome measure was defined as the PDC during days 91-270 following the new depressive episode date. Utilizing processes used by other studies(50, 71), approaching adherence as "any" or adherence to "all" was considered. Individuals were allowed to be "adherent" for each day if they had at least one oral antihyperglycemic medication available to them on that day.

Furthermore, the duration of any hospitalization was excluded from the numerator and denominator in the PDC calculations. Hospitalizations were treated as immeasurable time because the administrative health databases used do not record inpatient drug use.(83) If an individual was hospitalized for >50% of the outcome assessment window, they were excluded because there was insufficient data to calculate a PDC.

4.2 Main Findings

Based on the above rationale, the goal of my thesis was to determine adherence to oral antihyperglycemic medications prior to a new depressive episode and whether treatment of depression impacts adherence to oral antihyperglycemics. Overall, it was found that a total of

165,056 (77%) new metformin users from 214,762 people were dispensed an oral antihyperglycemic medication. A total of 31,513 (19.1%) new metformin users had at least 1 depression-related service record after initiating metformin. A total of 17,385 (10.5%) individuals had their first depression-related service record at least one year after starting metformin. The mean duration between metformin initiation and a new episode of depression was 3.0 (SD 1.6) years.

The mean PDC in the year before new depressive episode was significantly lower for individuals with a depressive episode at 0.61 compared to controls at 0.63. After adjusting for other confounders, individuals with a depressive episode were more likely to have poor adherence compared to controls with an odds ratio of 1.21 (95%CI 1.17,1.26). More participants with depression (9,382, 54.0%) had poor adherence compared to controls (58,731, 51.5%) ($p<0.001$). When taking the analysis one step further to examine trajectory models, 4 trajectories of poor adherence were identified and one trajectory of good adherence to metformin in the year before a depressive episode. A higher proportion of individuals with depression were more likely to be in one of the four trajectories of poor adherence compared to controls (adjusted odds ratio 1.24; 95% CI 1.19-1.29). Four sensitivity analyses including multivariable models on all covariables, participants with a baseline HbA1c, excluding prevalent depression and excluding participants using adherence aids produced adjusted odds ratios that were similar in magnitude, direction, and statistical significance to the main logistic regression model. These findings are consistent with the hypothesis that people with a depressive episode would be more likely to have poor adherence in the preceding year, confirming that adherence is affected earlier than currently reported in the literature. This highlights that poor adherence may be an important factor to consider when assessing for early warning signs of depression.

In Chapter 3, a total of 7,220 (22.9%) had their first health service record for depression a minimum of one year after starting metformin, had at least 1 year before their study exit date, had no antidepressant dispensations in the previous 6 months and were not hospitalized for >50% of the outcome assessment window. There were 1,899 (26.3%) people that received ≥2 dispensations for antidepressants within 90 days of the new depressive episode.

The mean proportion of days covered was higher for the treated group (57%) compared to controls (55%); however, this difference was not statistically significant. There was a small, but non-significant difference in the proportions with poor adherence in the treated group (1,021, 53.8%) compared to controls (2,938, 55.2%) (p=0.28). After adjusting for other comorbidities and characteristics at baseline, pharmacologically treated depression was associated with a lower, but non-significant likelihood of poor adherence compared to no pharmacologic treatment with an odds ratio of 0.91 (95%CI 0.81,1.02). The first sensitivity analysis of forward selection modelling showed pharmacologic treatment of depression was significantly associated with a lower likelihood of poor adherence after adjusting for differences in demographic variables, comorbidities, and health service visit frequencies (adjusted odds ratio 0.86; 95%CI 0.77, 0.96). When adding cardiovascular and medications for other chronic conditions to the model, the association was no longer statistically significant (adjusted odds ratio 0.91;95%CI 0.81, 1.02). The remaining sensitivity analyses, including increasing the exposure assessment interval to 180 days, increasing the threshold for poor adherence to <90% and conducting multivariable model on subgroup of individuals with an available HbA1c produced results consistent to the main analysis. However, defining poor adherence using the median split of PDC at 0.67 produced an adjusted odds ratio similar in magnitude and direction but the association was statistically significant (adjusted odds ratio 0.86; 95% CI 0.77, 0.96).

4.3 Limitations

I have suggested, through my two projects, the importance of monitoring patients living with diabetes for early symptoms of depression to minimize potential suboptimal adherence to medications, as well as to initiate interventions to treat depression as appropriate. However, I recognize the limitations that need to be taken into account when interpreting the results of my thesis, including:

1) Given that an observational study design was used, the study is limited in ability to determine a causal link between depression and poor adherence or treated depression and poor adherence. The design does not enable us to eliminate the possibility of selection bias or confounding that may have not been measured; however, the risk of bias or confounding was minimized by controlling for factors that were measurable or identifiable including demographics, comorbidities, clinician visits, hospitalizations and duration of diabetes.
2) Administrative databases do not allow for ability to determine failure to fill an initial prescription. Primary non-adherence could not be identified, which may have led to underestimation of association between depression and adherence.
3) A dispensing record was assumed to mean the medication supply was obtained and consumed. This assumption of medication actually being consumed would overestimate the outcome if people do not use the medications received from pharmacies. Although the indirect measure of adherence from claims data may not be considered the most accurate and reliable, studies have found significant associations between adherence measured from refill information and other methods such as surveys, individuals' self-report, and pill counts.(72)

4) In addition, it was unknown whether patients receiving 7, 14- or 28-days supplies were in fact on adherence aids. Individuals receiving such consistent claims are more likely to be on adherence aids since they are commonly billed in weekly, biweekly or monthly intervals at the pharmacy. Those receiving adherence aids may overinflate the adherence rates of the general study population not receiving them. The sensitivity analysis in Chapter 2 revealed no significant deviation from the main results when those assumed to be on adherence aids were removed from the study sample.
5) Administrative data also do not contain clinical progress notes or any information on symptomology. Information on the onset, severity, and characteristics of the depressive episode were not available to determine reduced willingness or capability of capacity to take medications.
6) Given the nature of claims data using ICD coding, risk of misclassification by clinicians in the administrative data could have occurred. Clinicians may have also missed clinically relevant depression symptoms, under-diagnosing depression and, in turn, leading to underestimation of the number of depression cases. This is also relevant for the other comorbidities that were analyzed for confounding variables. Misclassification was minimized by selecting ICD codes with strong positive predictive values reported in literature.
7) Measuring adherence using calculations such as proportion of days covered assumes individuals have the same patterns of adherence over time, which may not be true. However, this was accounted for by using a second measure of adherence—adherence trajectories. Adherence trajectories help identify variable patterns of adherence given that medication taking is a dynamic behavior and may change over time.(73)

8) Hospitalizations were excluded from the outcome measure of adherence because there is no information on medication taking during admissions in the administrative database. This limitation was recognized, and hospitalizations were treated as immeasurable time, by excluding those patients who were hospitalized for more than 50% of the outcome assessment period. This may have underestimated the outcome of adherence. However, given the small number of individuals hospitalized in each project, underestimation was likely not a concern.

4.4 Implications for Clinical Practice and Regulatory Agencies

World Health Organization reports adherence to medications in developed countries to be an estimated average of 50%.(65) Adherence rates also vary from 43-78% in clinical trials and are suboptimal to what is considered good adherence.(74) Medication non-adherence is a major concern to regulatory agencies and clinical practice due to increased risk of morbidity, mortality and health care costs.(75, 76) Therefore, measuring adherence to medications is vital for stakeholders, such as policy makers. Likewise, adherence to medications is a critical aspect of providing optimal patient care by clinicians.

The results of my research revealed poor adherence to oral antihyperglycemic medications in the year leading up to a depressive episode. These results are highly generalizable to the population of Alberta, and likely to others within Canada, given the large study population I was able to include for analysis by using administrative data.(96) This highlights the need to regularly screen individuals with diabetes for depression to prevent its contribution to non-adherence to medications necessary to manage diabetes. Specifically, declining or poor adherence to antihyperglycemics could be a signal to clinicians that depressive symptoms may be present. Likewise, my results suggest that pharmacological treatment for depression, if

diagnosed, may potentially help reduce poor adherence. While further research is needed to explore the relationship between depression treatment and adherence, the magnitude of the association I found may be an important signal that warrants consideration. Regulatory agencies would benefit from improved depression screening and interventions in those with diabetes as better adherence to oral antihyperglycemic medications can contribute to lower health care resource utilization from decreased incidence of diabetes complications and related hospitalizations.(77, 78) Indeed, improved adherence decreases health care costs and increases patients' quality of life.(79)

Pharmacists are front-line clinicians that are easily accessible to the public who could be a useful resource in implementing screening for depression into their clinical practice. Screening for depression in their patients with diabetes could potentially help increase optimal medication taking behaviors through creating opportunities for shared decision-making. More specifically, pharmacists can easily use adherence patterns within their electronic software to identify those patients with diabetes who are non-adherent or with patterns of recent decline in adherence. Pharmacists will in turn be able to deliver optimal patient centered care to improve clinical outcomes using their full scope of practice, as well as collaborate with other health professionals caring for a patient. In addition to pharmacists, other clinicians would likely benefit from adherence assessment and discussions with their patients, including physicians and nurse practitioners.

4.5 Future Research

Areas of future research to continue exploring the association between diabetes, depression and adherence may include:

1) Exploring adherence trajectories before and after depression diagnosis; this could identify how patterns of adherence in individuals with type 2 diabetes change in the context of concurrent depression. Further research needs to be conducted using more than a single measure of adherence to identify the impact of medication non-adherence on health care costs and utilization. There is vast literature on such matter using a single adherence measure that assumes all individuals have homogeneous patterns of medication taking behaviors.(80, 81) However, quality reporting measures that inform health system interventions, their effectiveness and in turn costs/utilization of health care based on these homogeneous measures of adherence may mask the important implications from distinct patterns of medication taking behaviors.
2) Examining adherence trajectories to identify characteristics of individuals belonging to distinct patterns of adherence; results may help clinicians better monitor and intervene in the care of patients who may possess similar, and perhaps distinct, characteristics.
3) Also, adherence trajectories should be examined to determine clinical outcomes of individuals in various patterns of adherence. This has been documented in a previous study examining hospitalizations and emergency department visits in variable trajectories of adherence using administrative data.(61) Patterns of adherence could then be used in clinical practice as a signal to prevent or reduce the risk of negative clinical outcomes (e.g., microvascular complications).
4) Further research stemming from this thesis should determine how to capture non-pharmacological treatments for depression in administrative data and examine how non-pharmacological treatments impact adherence to antihyperglycemic medications. Perhaps

future research should focus on the creation of a registry for comprehensive depression treatments, which would greatly benefit both research and regulatory agencies.

5) Research could further dive into examining the impact of adherence to antidepressants on clinical outcomes (e.g., glycemic control, weight management, reduction in complications) to determine whether treatment of depression leads to better health outcomes in diabetes.
6) Knowledge translation around the matter of clinically relevant depressive symptoms and adherence to oral antihyperglycemic medications needs to be extended to all clinicians. For example, pharmacists are a valuable and easily accessible resource for patients how can help with screening for depressive symptoms. Future research could examine the impact of pharmacist intervention on identification and management of depressive episodes.
7) Uptake of depression screening tools is required to assist clinicians in screening for depression regularly in their own clinical practice and to encourage regular follow-up once treatment of depression is initiated. Identifying approaches on how to implement these tools may help clinicians build these into practice.
8) Adherence assessment in the study was based on refill information from prescription claims data; hence, the study makes the assumption that the prescriptions filled by individuals were used appropriately. A validation study could be conducted to measure agreement between administrative data and actual medication consumption.

4.6 Conclusion

The accomplishments of this thesis work closed previous gaps in the literature exploring the nature of the association between diabetes, depression and adherence. In individuals with

type 2 diabetes, a lack of adherence to type 2 diabetes medications may serve as an early warning sign for the presence of comorbid depression. Although treatment of a new depressive episode appears to be associated with a lower likelihood of poor adherence, the observed association did not reach statistical significance. However, results of this thesis provide a signal highlighting the importance of treating depression in order to prevent poor adherence to antihyperglycemic medications and further complications associated with diabetes. The findings from two different, interconnected projects, suggest that by following adherence, clinicians may be able to identify people experiencing symptoms of depression earlier and intervene sooner to help potentially improve and support medication management of patients with type 2 diabetes.

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