The Association between Antidepressant Therapy and Glycemic Control in Patients with Diabetes: A Canadian Primary Care Cohort

Justin Gagnon, MA
Department of Family Medicine
McGill University, Montreal
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PREFACE

For my MSc thesis and manuscripts, I conceived of the topic of study, developed the methods, conducted the analyses, led the interpretation of results and wrote the text. My supervisors, Dr. Marie-Thérèse Lussier and Dr. Gillian Bartlett provided guidance throughout. Drs. Lussier and Bartlett, as well as Dr. Brenda MacGibbon and Dr. Stella Daskalopoulou revised the written content. The research topic was conceived during my employ as Research Assistant with the Canadian Primary Care Sentinel Surveillance Network, under the supervision of Dr. Marie-Thérèse Lussier. All authors have approved the final version of the articles. The authors had no conflicts of interest to report.

The findings of this research were presented at St-Mary's Hospital Grand Rounds in Montreal, Canada (June 2015); the North American Primary Care Research Group (NAPCRG) Annual Meeting in Cancun, Mexico (October 2015); the Family Medicine Forum (FMF) in Toronto, Canada (November 2015); and the McGill University Family Medicine Research Division and Graduate Student Society Symposium in Montreal, Canada (May 2016).

I was granted the following travel awards to present my research: CIHR Travel Award to attend the NAPCRG Annual Meeting in Cancun, Mexico (October 2015); and the McGill Department of Family Medicine Academic Excellence Research Award to attend the Family Medicine Forum in Toronto, Canada (November 2015).

THESIS ABSTRACT

Context: Antidepressants (AD) are among the most prescribed medications in Canada. Research has found an association between certain ADs and impaired glycemic control, which contributes to an increase in risk of complications for people with diabetes. Evidence on the impact of different ADs on glucose metabolism is inconclusive as studies in this area are largely heterogeneous and find contradictory or non-significant results. The objectives of this research are to describe the prescription of ADs for people with diabetes in Canada, and measure the impact of the most commonly prescribed ADs on glycemic control.

Methods: A retrospective cohort study was conducted using primary care electronic medical records collected by the Canadian Primary Care Sentinel Surveillance Network (CPCSSN). The CPCSSN dataset used in this research comprised the electronic medical records extracted in September of 2014 from 115 primary care practices across Canada. Descriptive statistics were used to describe the prescription of ADs for people with diabetes. A generalized linear mixed (GLM) model was computed to estimate the impact of the five most commonly prescribed ADs on HbA1c.

Results: In 2014, the most commonly prescribed ADs for people with diabetes were, in order of frequency, Citalopram (16.6%), Amitriptyline (16.2%), Venlafaxine (15.7%), Trazodone (14.2%) and Escitalopram (12.4%). Estimates for the impact of ADs on HbA1c generated by the GLM model were reported in terms of mean HbA1c ratios relative to Citalopram, the most commonly prescribed AD. Overall, the impact of Amitriptyline, Venlafaxine, Trazodone and Escitalopram on HbA1c did not differ significantly from Citalopram. Sensitivity analyses examining the impact of the ADs on HbA1c for different periods of exposure showed a tendency of lower HbA1c between 6 and 12 months of exposure

for Trazodone (0.95; 95% CI=0.88 to 1.04) and Escitalopram (0.93; 95% CI=0.84 to 1.03) relative to Citalopram.

Discussion: The results of this research suggest that for prolonged use, Trazodone and Escitalopram may be more effective than Citalopram, the most prescribed AD, for people with diabetes. Future research should seek to confirm these findings, examine the dose-response relationship between ADs and change in HbA1c, and control for depression severity and weight change.

Conclusion: This appears to be the first pan-Canadian epidemiological study of primary care practices describing the prescription of ADs for people with diabetes. This is also one of few epidemiological studies conducted using electronic medical records which examine the impact of ADs on HbA1c using robust statistical analyses for repeated measures which take into account within- and between-subject variation over time.

RÉSUMÉ

Contexte : Les antidépresseurs (AD) sont parmi les médicaments les plus prescrits au Canada. Des études rapportent que certains AD sont associés à un mauvais contrôle de la glycémie, ce qui pose un risque pour les personnes atteintes de diabète. Les études sur l'impact des différents AD sur le métabolisme du glucose sont peu concluantes, à cause du fait que les devis de recherche dans ce domaine sont largement hétérogènes et trouvent des résultats contradictoires ou non-significatifs. Les objectifs de cette recherche sont : de décrire la prescription d'ADs pour les personnes atteintes de diabète au Canada, et de mesurer l'impact des AD les plus fréquemment prescrits sur l'hémoglobine glyquée (HbA1c).

Méthodes : Une étude de cohorte rétrospective de dossiers médicaux électroniques de première ligne provenant du *Réseau canadien de surveillance sentinelle en soins primaires des pratiques* (RCSSSP) a été menée. La base de données du RCSSSP utilisée dans ce projet a été constituée à partir des dossiers médicaux électroniques extraites en septembre 2014 de 115 pratiques de première ligne à travers le Canada. Des statistiques descriptives ont été utilisées pour décrire la prescription d'ADs chez les personnes atteintes de diabète. Un modèle linéaire généralisé mixte a été calculé pour estimer l'impact des cinq ADs les plus fréquemment prescrits sur l'HbA1c.

Résultats : En 2014, les ADs les plus fréquemment prescrits pour les personnes atteintes de diabète étaient, en ordre de fréquence, le Citalopram (16,6%), l'Amitriptyline (16,2%), la Venlafaxine (15,7%), le Trazodone (14,2%) et l'Escitalopram (12,4%). Les estimations de l'impact des AD sur l'HbA1c générés par le modèle sont rapportés sous forme de ratio d'HbA1c moyenne relatif à Citalopram, l'AD le plus fréquemment préscrit. Dans l'ensemble, aucune difference significative a été trouvée pour l'effet de l'Amitriptyline, la Venlafaxine, le Trazodone

and l'Escitalopram sur l'HbA1c par rapport à Citalopram. Des analyses de sensibilité examinant l'impact des ADs sur l'HbA1c pour des différentes periodes d'exposition ont montré une tendance d'HbA1c moins élevée pour le Trazodone (0,95; 95% IC=0.88 à 1.04) et l'Escitalopram (0,93; IC à 95% =0,84 à 1,03) par rapport au Citalopram.

Discussion : Les résultats de cette étude suggèrent que pour une utilisation prolongée, le Trazodone et l'Escitalopram sont potentiellement plus efficaces que le Citalopram chez personnes atteintes de diabète. Les recherches futures devraient chercher à confirmer ces résultats, examiner la relation dose-effet entre les AD et le changement de l'HbA1c, et contrôler pour la sévérité de la dépression et le changement de poids.

Conclusion : Ceci semble être la première étude épidémiologique pancanadienne de pratiques de première ligne décrivant la prescription d'ADs chez les personnes atteintes de diabète. Ceci est aussi l'une des seules études épidémiologiques qui examinent l'impact des AD sur l'HbA1c qui utilisent les dossiers médicaux électroniques ainsi que des statistiques robustes pour l'analyse de mesures répétées qui tient compte des variations intra- et inter-sujet à travers le temps.

ABBREVIATIONS

AD – Antidepressant

AIC – Akaike Information Criterion

ATC – Anatomical Therapeutic Chemical

CDA – Canadian Diabetes Association

CPCSSN – Canadian Primary Care Sentinel Surveillance Network

CVD – Cardiovascular disease

DM – Diabetes Mellitus

DSM – Diagnostic and Statistical Manual of Mental Disorders

EMR – Electronic Medical Records

FP – Family Physician

GLM – Generalized Linear Mixed [model]

HbA1c – Glycated Hemoglobin

HPA – Hypothalamic-Pituitary-Adrenal [axis]

ICD – International Statistical Classification of Diseases and Related Health Problems

MDD – Major Depressive Disorder

NaSSA – Noradrenergic and Specific Serotonergic Antidepressant

NDRI – Norepinephrine-Dopamine Reuptake Inhibitor

PHC – Primary Health Care

RCSSSP – Réseau Canadien de surveillance sentinelle en soins primaires

RCT – Randomized Controlled Trial

SARI – Serotonin Antagonist and Reuptake Inhibitor

SNRI – Serotonin-Norepinephrine Reuptake Inhibitor

SSRI – Selective Serotonin Reuptake Inhibitor

T1DM – Type 1 diabetes mellitus

T2DM – Type 2 Diabetes Mellitus

TCA – Tricyclic Antidepressant

WHO – World Health Organization

TABLES AND FIGURES

INTRODUCTION

Diabetes is one of the most prevalent chronic diseases in Canada and worldwide. The Public Health Agency of Canada estimates that over 2.5 million Canadians currently live with diabetes (1) and these numbers are expected to increase (2). Depression, a common comorbidity in people with diabetes, can increase the risk of poor blood sugar control (3). What is more, people suffering from diabetes and comorbid depression are at greater risk of developing cardiovascular disease (CVD) and suffering complications than those with either condition alone (4-9). The relationship between depression and diabetes is bidirectional. Depression is associated with a decline in self-management behaviours (6, 10-12) and pathophysiology linked to impaired glucose metabolism (13); and people with diabetes are at increased risk of depression (14). In Canada, an estimated 11% of adults will experience at least one depressive episode at some point in their lifetime (15). In people with type 2 diabetes (T2DM), the estimated lifetime prevalence of depression is between 24% and 29% (16-18).

Treatment of depression is important for reducing the risk of CVD and complications in people with diabetes and depression; however, some antidepressants (AD) may affect glucose metabolism and mediate the risk of poor diabetes control, independent of depression. Some ADs are purported to impair glucose metabolism; whereas others are purported to improve it (19). At present, evidence in this field is inconclusive (19, 20). The results of clinical trials and epidemiological studies are inconsistent and are seldom replicated. The inconsistency of findings between studies is largely explained by the heterogeneity of sample populations and study designs (3, 20-22). Clinical trials are often conducted using small, select populations, observed for short periods of time. Epidemiological studies often permit longer study periods in larger populations; however, the study subjects tend to be relatively heterogeneous. Individual factors

such as genetics, metabolism, self-care behaviours and social circumstances and the severity of depressive symptoms can mediate to varying degrees the relationship between ADs and glycemic control in people with diabetes (23-25). Observational studies tend to look at long-term outcomes such as diabetes onset, whereas trials tend to look at short-term biological indicators of glycemic control such as glucose, insulin or glycated hemoglobin (HbA1c).

The results of trials suggest some ADs are linked to impaired glucose metabolism, either directly, or indirectly through weight gain, which can cause insulin resistance and poor diabetes control; other ADs are linked to improved glucose metabolism and/or weight loss. ADs such as Amitriptyline (26), Nortriptyline (27), Mirtazapine (28-31) and Paroxetine (31) have been linked to weight gain. Other ADs, such as Duloxetine (32) and Imipramine (33), have been linked to impaired glucose metabolism. On the other hand, improved glucose metabolism has been reported for Citalopram (34, 35), Fluoxetine (34, 36), Sertraline (37), Bupropion (38) and (despite being linked to weight gain) Paroxetine (39) and Mirtazapine (28). These findings, however, have not been corroborated in epidemiological research (40-43) and other trials (39, 44-46).

Some observational studies have linked specific pharmacological classes of ADs such as selective-serotonin reuptake inhibitors (SSRI) (47), serotonin-norpinephrine reuptake inhibitors (SNRI) (47), tricyclic ADs (TCA) (47), as well as AD use in general (48-53), to increased risk of T2DM onset. Other studies did not find a significant association between AD use and change T2DM onset risk (54-57). Few observational studies have examined the long-term impact of individual ADs on glycemic control in people with diabetes.

Further research on the long-term impact of individual ADs on glucose metabolism in people with diabetes is needed. Additionally, given the important risk ADs may pose, especially

for people with diabetes, knowledge about the prescription of ADs in Canada for people with diabetes is also vital. Therefore, the objectives of this research are to describe the prescription of ADs for people with diabetes in Canada and estimate the effect of AD medications on glycemic control in people with diabetes.

LITERATURE REVIEW

Diabetes

Diabetes mellitus is a chronic condition characterized by either reduced insulin production or impaired insulin function. The two primary forms of diabetes mellitus are *type 1* (T1DM) and *type 2* (T2DM). T1DM occurs when the immune system mistakes beta cells (insulin-producing cells) as foreign bodies and attacks them (58). Consequently, the body releases little or no insulin. Without insulin, the body cannot effectively use glucose for energy nor effectively regulate blood glucose levels (58). Individuals suffering from this type of diabetes are treated with insulin to compensate for the body's limited production.

T2DM diabetes is typically characterized by insulin resistance which, over time, can lead to decreased insulin secretion and increased glucose production by the liver (59). T2DM begins with insulin resistance, whereby cells in the body gradually become less effective at using insulin to effectively to reduce circulating glucose levels (60). While there appears to be a genetic component, abdominal obesity (excess fatty tissue) is the most common factor associated with insulin resistance (60). When insulin resistance develops, the body typically tries to compensate by instructing the beta cells to secrete more insulin and the liver to release more glucose. Higher insulin secretion rates cannot generally be sustained over long periods of time and can consequently result in permanent impairment of beta cell function and decreased insulin

secretion (59). Primary risk factors for T2DM include obesity, fat distribution around the abdomen and physical inactivity (58). These are also all independent risk factors for cardiovascular disease (61).

The prevalence of diabetes among Canadian primary care patients is estimated at 7.6% (62). Approximately 90% of people with diabetes suffer from T2DM and 10% from T1DM (63). The Canadian Diabetes Association (CDA) clinical practice guidelines provide the following criteria for a diagnosis of diabetes: $\geq$ 7 mmol/L fasting plasma glucose or $\geq$ 11 mmol/L two-hour plasma glucose in a 75g oral glucose tolerance test or $\geq$ 11 mmol/L plasma glucose at any time of day with symptoms of diabetes (such as frequent urination, abnormal thirst and unexplained weight loss) (64). T1DM is diagnosed by testing for markers of autoimmune destruction of beta-cells such as islet cell antibodies and insulin autoantibodies (65).

Prolonged excess levels of glucose in the blood can damage blood vessels, nerves and organs. Complications of uncontrolled diabetes include: peripheral neuropathy, kidney disease, high blood pressure, retinopathy, erectile dysfunction, heart attack and stroke (9). In people with T1DM or T2DM, the CDA recommends that medication therapy achieve a glycated hemoglobin (HbA1c) target value of less than 7% in order to reduce the risk of complications (66). The CDA recommends this the measure of glycemic control as it provides a reliable estimate of mean plasma glucose over the previous 3 to 4 months (67).

In terms of diabetes treatment for people with new diagnoses of T2DM, they recommend a combination of lifestyle management, such as diet and exercise, and initiation of metformin, an oral antihyperglycemic medication of the pharmacological class Biguanides (68). If HbA1c levels remain above 8.5%, then other oral medications may be added in combination until this target is met. Other classes of oral medications prescribed for the management of diabetes

include: Sulfonylureas, Thiazolidinediones, Dipeptidyl peptidase 4 inhibitors, Alpha glucosidase inhibitors and combinations of glucose lowering drugs (69). If the target is not achieved with a combination of oral medications, then recommended treatment consists of providing a combination of basal insulin and fast-acting insulin (70).

Depression

Depression is broadly characterized by a state of low mood and aversion to activity affecting a person's thoughts, behaviours and sense of well-being (71). A clinical diagnosis of depression is made based on the patient's self-reported experiences, reports from relatives and friends, and mental status examination. The criteria for the diagnosis of major depressive disorder (MDD) provided in the Diagnostic and Statistical Manual version 5 (DSM-V) consists of presentation of five or more of the following symptoms (and at least one of the first two): depressed mood; loss of interest or pleasure; significant weight loss when not dieting or weight gain; insomnia or hypersomnia; psychomotor agitation or retardation; fatigue or loss of energy; and feelings of worthlessness or excessive guilt (72). Depression is most commonly diagnosed and treated in primary care (73-75).

The lifetime prevalence of depression in the Canadian population aged 15 years and over is estimated at 11%, and the point prevalence is estimated at 5% (76). Depression is a multi-faceted disorder that manifests itself in different ways and has been associated with diverse causes. Risk factors for depression include heredity, personality traits (low self-esteem, anxiety, and pessimism), abuse, trauma, stigma, drug dependence, a number of chronic illnesses and certain medications. Recovery time for major depressive episodes is estimated at 8.4 months on average, with 20% of episodes lasting longer than 2 years (77). Professional care, compared with

no care, typically shortens recovery time (77). Additionally, pharmacological treatment and combined psychotherapy and pharmacotherapy alone are more effective than psychotherapy alone (78).

Uncertainty still surrounds the pathophysiological mechanisms of depression. Much of what is known about the mechanisms of depression comes from the discovery of pharmacological agents that improved symptoms of mood disorder (79). Research found that these early ADs (tricyclic antidepressants – TCAs - and mono-amine oxidase inhibitors – MAO-I) increased synaptic levels of the monoamine neurotransmitter serotonin. This observation led to the *monoamine hypothesis* of depression, which supposes that the root cause of depression is the deficit of certain neurotransmitters (80). Other more recent and popular hypotheses include: the dysfunction of glutamate signaling in the brain (leading to impaired synaptic transmission and impaired neuroplasticity); and impaired plasticity of neuronal circuits specifically linked to the hippocampus, which is involved in the regulation of mood. Numerous additional hypotheses have also been proposed. Most developments in AD fabrication have sought to improve the tolerability of the early ADs, which led to the development of selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors (SNRI). Further developments aimed at improving efficacy and/or reducing the time of onset of SSRIs and SNRIs through combination with other molecules (79). ADs generally target the neurotransmitters serotonin, dopamine and norepinephrine (to varying degrees) and in the last decade there has been increased interest in targeting glutamate transmission.

The Canadian Network for Mood and Anxiety Treatments (CANMAT) distinguishes two phases of major depressive disorder treatment: the acute phase and the maintenance phase (81). The goal of acute treatment is the resolution of depressive symptoms and maintenance involves

preventing recurrence. The CANMAT recommends a combination of psychotherapy and antidepressant medication for both acute and maintenance phases of MDD (82). While a combination of pharmacotherapy and psychotherapy is recommended for treatment of depression, which has been found to be effective in 60% to 80% of depressed patients, fewer than 25% of those affected have access to effective treatment (83). What is more, up to 40% of patients are resistant to pharmacological treatment (83). Psychotherapy is often quite costly and is largely inaccessible for people suffering from depression, therefore in most cases depression is treated with ADs alone (84).

Pharmacological treatment of depression

The typical pharmacological classes of ADs are: selective serotonin reuptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitors (SNRI), tricyclic antidepressants (TCA), serotonin antagonist reuptake inhibitors (SARI), norepinephrine-dopamine reuptake inhibitors (NDRI), noradrenergic and specific serotonergic antidepressants (NaSSA) and monoamine oxidase inhibitors (MAO-I) (85). Efficacy studies generally find ADs are more effective at treating depressive symptoms than placebos (86) and while ADs are relatively comparable in terms of treatment of depressive symptoms, findings indicate some medications may be more efficacious and acceptable than others (87).

In a recent cross-sectional study of primary care practices across Canada, Wong et al. (2014) describe the prescription of ADs by pharmacological class. They reported that the most frequently prescribed AD medication classes are SSRIs and SNRIs (88). With regard to individual AD agents, there is a lack of information in the literature on the frequency of AD prescription in Canada. A description of individual AD prescription in Quebec was published in

2011 by the *Conseil du médicament*, however. They reported that between 2005 and 2009 the most prescribed ADs were (in terms of numbers of new users): Citalopram (SSRI), Amitriptyline (TCA), Venlafaxine (SNRI), Trazodone (SARI), and Paroxetine (SSRI), respectively (89). No information was found on the prescription of ADs for people with diabetes in Canada, by individual AD or by pharmacological class.

Comorbid diabetes and depression

People with type 2 diabetes are twice as likely to suffer from depression compared to those without (90-93). People with depression are 30% more likely to suffer from T2DM compared with those without depression (94, 95). Approximately 24% to 29% of people with T2DM will suffer from depression at some point in their lives (16-18) and an estimated 10% to 15% of people with T2DM currently suffer from depression (92, 93). The relationship between diabetes and depression is attributed to behavioural, psychological and biological factors.

In terms of biological factors, the relationship between depression and diabetes is complex. Biochemical states associated with depression have been linked to impaired glucose metabolism; and states associated with diabetes have been linked to the development of depressive symptoms. Researchers posit that the bi-directional relationship between depression and diabetes involves immune and inflammatory responses, the hypothalamic-pituitary-adrenal (HPA) axis, and insulin resistance (96). Researchers have found increased inflammatory cytokine production (97, 98) and elevated levels of stress hormones cortisol and adrenaline in people suffering from depression. Chronically elevated concentrations of inflammatory cytokines contribute to insulin resistance and a decrease in the number of beta cells (19). Increased

cytokine concentrations are also associated with activation of the HPA axis, which leads to glucocorticoid and adrenaline secretion by the adrenal glands. Glucocorticoids are hormones that replenish energy stores during periods of stress by increasing glucose production by the liver and inhibiting glucose uptake in muscle and adipose tissue (98). Increased levels of adrenaline cause the body to release stored glucose and fat, to use as energy. Chronic stress leads to hypercortisolaemia, which contributes to increased insulin resistance, promotes sugar and fat cravings and increases abdominal fat retention, all of which interfere with normal glucose metabolism (98). If cells become too resistant to insulin or if the body is no longer able to produce sufficient quantities of insulin, glucose cannot be effectively used and blood glucose levels will remain elevated. Elevated blood sugar is associated with increased levels of the neurotransmitter glutamate, which can result in a dysregulation of emotions, contributing to feelings of depression (99). In addition to this cyclical relationship, living with diabetes – a chronic disease necessitating serious engagement and lifestyle change – can be for many people a demanding psychological burden that further contributes the manifestation of depressive symptoms (96).

In addition, depression is associated with a decline in self-care behaviours and physical activity (6, 10, 11, 23). People suffering from depression are less likely to take their medications, sufficiently engage in physical activity, and eat the types and quantities of foods recommended (100, 101). They are also less likely to monitor their blood sugar and seek medical assistance when needed (101). The decline in self-care behaviours typically observed in people suffering from depression increases the risk of hyperglycemia and poor glycemic control in people with diabetes (24, 102, 103).

T2DM and depression share a number of environmental and lifestyle factors such as high body-mass index (BMI), poor diet, low levels of physical activity, and smoking (96). Both conditions may be exacerbated by the presence of these factors. In addition, depression and diabetes also vary according to biological factors such as age and sex. Increased age is a major risk factor for T2DM (104). Depression, on the other hand, is less prevalent among older adults compared with younger adults, and presentation and severity of depression tends to differ significantly between them (105). Diabetes is most prevalent among men for all age groups (62) and depression is most prevalent among women than men (106). Finally, the presence of cardio-metabolic comorbidities such as obesity, hypertension and dyslipidemia may also contribute to depression and poor glycemic control (104).

Antidepressants and diabetes

Evidence on the effects of ADs on glycemic control is inconsistent. This inconsistency is due in large part to the heterogeneity of research on this topic, specifically in terms of study designs, sample populations, exposures and outcomes. Current knowledge comes from clinical trials and epidemiological research. Clinical trials comprise primarily a comparison of two medications or comparison of one medication with a placebo control group (19, 20). Observation periods tend to be relatively short (<6 months) and sample size is often relatively small (<100 people) (19, 20). Exposure variables consist primarily of individual ADs at a specific range of dosage. Primary outcomes comprise measures of glucose metabolism, such as fasting glucose, fasting insulin, glucose tolerance and HbA1c, as well as weight, which can have an impact on glucose metabolism. Epidemiological or observational research, which comprises cohort, case-control and case reports, tends to involve an examination of more heterogeneous, larger

populations over longer observation periods, compared to trials. Exposure variables largely consist of either ADs grouped by pharmacological class, or AD use in general. Observational research examining the impact of individual ADs is scant. The primary outcome of observational studies in this field consists of diabetes onset. Measures of glucose metabolism such as HbA1c, insulin resistance, fasting glucose and/or glucose tolerance are less often studied.

Evidence from clinical trials

In a meta-analysis of randomized controlled trials (RCTs), McIntyre et al. (2006) reported that serotonergic ADs (i.e. SSRIs and SARIs) appear to reduce hyperglycemia, normalize glucose homeostasis and increase insulin sensitivity; whereas noradrenergic ADs (i.e. TCAs) had the opposite effect (19). No significant disruption in glucose homeostasis was observed with newer dual-mechanism ADs (i.e. SNRIs, NDRI and NaSSA), on which less research has been conducted. Another more recent meta-analysis of RCTs by Hennings et al. (2012) reported similar findings: SSRIs and SARIs appeared to improve glucose metabolism and TCAs appeared to ADs impair glucose metabolism (20). Additionally, they reported an association between certain dual-mechanism ADs (i.e. SNRIs) and impaired glucose metabolism. No significant associations between Bupropion (NDRI) or Mirtazapine (NaSSA) and changes in glucose metabolism were found. In these syntheses, findings from trials examining the effects of individual medications were grouped by pharmacological class; however, individual ADs within the same class can have varied actions and impact glucose metabolism differently (107). Findings involving individual medications may not be generalizable to the level of pharmacological class.

With regard to individual medications, recent trials have reported that the TCA Imipramine (33) and the SNRI Duloxetine (32) were associated with an increase in fasting glucose. A greater number of studies have reported no significant association between ADs and glucose metabolism, however. No significant association was found for the TCAs Impramine (33) and Nortriptyline (27, 108); the SNRIs Duloxetine (44) and Venlafaxine (26); the NaSSA Mirtazapine (29, 30, 44); and the SSRIs Fluoxetine (27, 44), Citalopram (109), Paroxetine (39) and Escitalopram (110). With HbA1c as the outcome, no significant association was found for the TCA Nortriptyline (108); the SNRIs Duloxetine (32, 44) and Venlafaxine (26); the NDRI Bupropion (111); and the SSRIs Sertraline (112, 113), Fluoxetine (27, 45), Paroxetine (39, 114) and Escitalopram (110).

Weight gain, which is generally associated with increased risk of impaired glucose metabolism, was reported for the TCAs Amitriptyline (26) and Nortriptyline (27); and the NaSSA Mirtazapine (28-30). No significant association with weight was observed for the SSRIs Fluoxetine (27, 44, 45), Paroxetine (39, 46), Citalopram (109) and Sertraline (37); SNRIs Duloxetine (44) and Venlafaxine (26); the NaSSA Mirtazapine (44) and the NDRI Bupropion.

With regard to improved glucose metabolism, decreases in fasting glucose been observed with SSRIs Citalopram (34, 35) and Fluoxetine (34, 36); NaSSA Mirtazapine (28); and NDRI Bupropion (38). Decreases in HbA1c have been observed with Citalopram (34), Fluoxetine (34) and Sertraline (37, 113). Weight loss has been reported with SSRIs Citalopram (35) and Fluoxetine (115); SNRI Duloxetine (32); and NDRI Bupropion (38, 116).

In sum, evidence from trials suggests SSRIs, NDRIs and NaSSAs may be associated with improved glucose metabolism; and TCAs and SNRIs may be associated with impaired glucose metabolism. In addition, SSRIs, NDRIs and SNRIs may be associated with weight loss; TCAs

and NaSSAs may be associated with weight gain. The effects observed for individual AD agents may not be generalizable to their pharmacological class, however, and a greater number of studies have not been able to corroborate these findings. Few trials have examined the effects of the Trazodone, a SARI, on glucose metabolism.

Evidence from epidemiological studies

In a meta-analysis of cohort and case-control studies looking at the association between AD use in general and diabetes onset, Bhattacharjee et al. (2013) found an increased risk of diabetes onset among AD users compared to those who did not use any ADs (22). Another meta-analysis of observational studies by Yoon et al. (2013) compared the risk of diabetes onset by class and individual medication. They found an increased risk of diabetes for both SSRIs and TCAs, with TCAs representing the highest risk (21). No significant increase in risk was observed for the other classes. In terms of individual medications, the SSRIs Paroxetine and Citalopram, and the SARI Trazodone were associated with increased risk of diabetes onset.

A number of observational studies have reported an association between AD use in general and increased risk of diabetes onset (49-51, 53, 117). In many of these studies, however, the impact of depression and AD use is not differentiated. Individual observational studies examining the impact of ADs group by class have reported an association between TCAs (47) and concurrent use of SSRIs and TCAs (54) and diabetes onset. Other observational studies did not find any significant risk of diabetes onset for SSRIs or TCAs (54), or AD use in general (55-57). In observational studies involving measures of glucose metabolism as a primary outcome, insulin resistance was associated with AD use in general (118). The majority, however, report no

significant association between AD use and change in HbA1c (41-43), plasma glucose levels (43, 49) or insulin use (91).

Potential mechanisms

With regard to mechanisms of action which might explain observed associations between certain ADs and glycemic control, uncertainty still surrounds the biological pathways of the different AD medications (19). Hypotheses involving biological pathways are generally proposed to explain results such as those presented above. Given that evidence suggests glucose levels are affected differently by different ADs, researchers have concluded that ADs differ in terms of their impact on glucose metabolism. Most ADs, including SSRIs, SNRIs, NaSSAs and TCAs, contribute through different pathways to increases in monoaminergic serotonin and norepinephrine and alter the balance of the hypothalamus-pituitary-adrenal (HPA) axis, which are associated with increased insulin resistance (44). ADs also modulate concentrations of inflammatory cytokines, which are also linked to depression and contribute to insulin resistance and a decrease in the number of beta cells (19). Importantly, ADs target (differently) hormones such as serotonin, dopamine and noradrenaline, which are directly involve in appetite regulation and the mediation of feeding behaviours (19). In addition, researchers have suggested that while ADs might alleviate symptoms of depression, a portion of the pathophysiology associated with depression and which impacts glucose metabolism may remain (19).

Summary

In sum, research on the impact of ADs on glycemic control is inconclusive at present. Much of what is known about the association between ADs and blood sugar control comes from clinical trials, which examine short-term effects in small, select populations. There is a lack of sufficiently powered observational studies examining the impact of individual ADs on biological measures of glycemic control in people with diabetes. Moreover, there is a lack of research describing the frequency with which individual ADs are prescribed for people with diabetes in Canada. Research on specific ADs is disproportionate to the frequency with which the ADs are prescribed. More research on the effects of the most frequently prescribed ADs is needed. The present research, therefore aims to answer the following research questions:

1. What is the frequency with which individual ADs are prescribed for people with diabetes in Canada?
2. What is the impact of the most frequently prescribed ADs on HbA1c in people with diabetes?

PREFACE TO MANUSCRIPT 1

This article, intended for publication in the Canadian Family Physician, provides a description of the prescription of antidepressant medications for primary care patients with diabetes in Canada. This objective was achieved through quantitative description of electronic medical record data from primary care practices across Canada collected by the Canadian Primary Care Sentinel Surveillance Network (CPCSSN) in 2014.

MANUSCRIPT ABSTRACT

Purpose: Depression is a common comorbidity in people with diabetes that increases the risk of poor diabetes control and diabetes-related complications. While treatment of depression is expected to reduce the risk of poor control, some ADs have been associated with impaired glucose metabolism. Research on the prescription of ADs for people with diabetes is lacking. The objective of this study is to describe the prescription of ADs for diabetic patients in Canada.

Methods: A cross-sectional study of electronic medical record data from 115 primary care practices across Canada was conducted. Data was obtained from the Canadian Primary Care Sentinel Surveillance Network (CPCSSN). Descriptive statistics were used to describe the prescription of antidepressants for people with diabetes between 2009 and 2014.

Results: The sample population consisted of 17,258 diabetic patients prescribed at least one antidepressant between 2009 and 2014. In terms of pharmacological class, the greatest proportion of people prescribed an AD were prescribed selective serotonin reuptake inhibitors (46.2%), followed by serotonin-norepinephrine reuptake inhibitors (24.3%) and tricyclic antidepressants (23.8%). The most frequently prescribed medications were Citalopram (16.6%), Amitriptyline (16.2%), Venlafaxine (15.7%), Trazodone (14.2%), Escitalopram (12.4%) and Bupropion (9.2%). The frequency of AD prescription varied in relation to sex and history of depression.

Conclusions: The present study provides a description of AD prescription in Canada for people with diabetes. This appears to be the first pan-Canadian epidemiological study of primary care practices describing the prescription of ADs for people with diabetes. The findings of this research are valuable as they provide insight into the implications of research evaluating the impact of ADs on glycemic control in people with diabetes.

ANTIDEPRESSANT PRESCRIPTION PRACTICES AMONG CANADIAN PRIMARY HEALTH CARE PROVIDERS FOR PATIENTS WITH DIABETES MELLITUS: AN EPIDEMIOLOGICAL STUDY USING ELECTRONIC MEDICAL RECORDS

Justin Gagnon, Marie-Thérèse Lussier, Brenda MacGibbon, Stella S. Daskalopoulou, Gillian Bartlett

Introduction

Depression is a common comorbidity in people with diabetes mellitus which increases the risk of macrovascular and microvascular complications (4, 5, 9). The relationship between depression and diabetes is bi-directional. People with diabetes are more likely to suffer from depression compared to those without diabetes (14) and depression is associated with poor glycemic control in people with diabetes (6, 13). Treatment of depression is expected to break this cycle, but recent evidence suggests that some antidepressants (AD) may further impair glucose metabolism, increasing the risk of poor glycemic control (19, 20). Given the risk ADs may pose, especially for people with diabetes, knowledge about the prescription of ADs for people with diabetes is needed.

At present, there is a lack of observational research describing the prescription frequency of ADs for people with diabetes in Canada (119). In a recent cross-sectional study, Wong et al. (2014) describe the prescription of ADs in a pan-Canadian primary care population with a history of depression (88), however AD prescription is grouped by pharmacological class. As ADs within the same pharmacological class may differ in terms of their impact on glucose metabolism (107), information on the prescription of individual AD agents is needed. The prescription frequency of individual ADs is reported in Quebec (89), but it is unknown whether

AD prescription in Quebec resembles that of Canada. It is also unknown whether AD prescription in a general Canadian population resembles the prescription of ADs for people with diabetes. The purpose of this study, therefore, is to describe the prescription of ADs in Canada for people with diabetes.

Methods

Data source and study population

The present cross-sectional study was conducted using primary care data extracted for public health surveillance and research purposes by the Canadian Primary Care Sentinel Surveillance Network (CPCSSN). At the time of the extraction for this research (September 30th 2014), the CPCSSN database comprised health records from 115 primary care practices in 7 Canadian provinces and 1 territory (Appendix I). The electronic medical records (EMR) of 985,176 patients were extracted, anonymized, cleaned, coded and centralized by the CPCSSN (120).

The present study sample comprises all *adult* (18 years of age and over) patients (n=66,617) with *diabetes* in the CPCSSN database at the time of extraction. From this sample, 5 annual cross-sections of diabetic patients prescribed ADs between October 1st 2009 and September 30th 2014 (n=17,258) were generated. This was further reduced to the 2014 cross-section (n=10,152) to reflect current prescription practices.

Diabetes

Diabetes cases were identified using the validated CPCSSN algorithm (Appendix I) that detects cases using a combination of information from patients' problem list, medication prescription records, laboratory results and billing (121). The diabetes case definition includes both type 1 diabetes (T1DM) and type 2 diabetes (T2DM). The case definition for diabetes has a sensitivity of 95.6 (93.4-97.9) and a specificity of 97.1 (96.3-97.9) (121). The study sample comprises patients identified as having diabetes at the time of data extraction.

Depression

Cases of *depression* were identified using a validated case detection algorithm (Appendix I) developed by the CPCSSN which combines information from patients' problem list, prescription records and billing. The case definition for depression includes depressive, bipolar and manic disorders. The algorithm detects *lifetime depression* (at least one occurrence of one of the above mood disorders). The CPCSSN case definition for depression has a sensitivity of 81.1 (77.2–85.0) and a specificity of 94.8 (93.7–95.9) (121).

Antidepressants

Medications in the patient health records were assigned World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) codes. Medications classed as *antidepressants* (ATC N06A) by the WHO Collaborating Centre for Drug Statistics Methodology (122) were included. The pharmacological classes reported here are: tricyclics (TCA); selective serotonin reuptake inhibitors (SSRI); serotonin-norepinephrine reuptake inhibitors (SNRI); serotonin

antagonist reuptake inhibitors (SARI); monoamine oxidase inhibitors (MAOI); norepinephrine-dopamine reuptake inhibitors (NDRI) and noradrenergic and specific serotonergic antidepressants (NaSSA).

ADs are classified according to the drug's molecular structure and/or the way they interfere with the serotonergic and norepinephrine neurotransmitter systems, rather than in terms of their receptor affinity and mechanisms of action (107). Therefore, the action of AD agents within the same pharmacological class can differ greatly and their impact on glucose metabolism may be distinct. AD prescription is therefore reported in terms of individual medication as well as by pharmacological class.

Other variables of interest

Patients are characterized in terms of age, sex, body mass index (BMI), concurrent health conditions, and diabetes medication prescription. Age at the date of extraction was computed using patients' dates of birth. A median BMI was computed for each patient using all BMI measures listed in their files. The median BMI was selected as a more reliable value (less susceptible to outliers) than the most recent measure or mean, given that a number of measures were suspected to be in error (outside the expected range and/or computed using weight in pounds rather than kilograms). Since BMI does not generally change a great deal over time (123), use of a fixed BMI measure is justifiable. The concurrent health conditions reported consist of conditions for which validated case definitions were developed by the CPCSSN: hypertension, depression, osteoarthritis, and chronic obstructive pulmonary disease (COPD). Diabetes medication prescription was identified using ATC classification. This information was categorically transformed to approximate diabetes type and severity: insulin only (T1DM), oral

diabetes medications only (non-insulin-dependent T2DM), and both insulin and oral diabetes medications (insulin-dependent T2DM).

Statistical analyses

The sample population is described using frequencies and proportions, and means and standard deviations, as appropriate. First, the characteristics of the sample of patients with diabetes and prescribed ADs in 2014 (n=10,152), stratified by sex, are reported. Second, AD prescription frequencies and proportions (by pharmacological class and individual AD agent) for the 2014 cross-section, stratified by sex and history of depression, are reported. Finally, as a sensitivity analysis, the frequencies and proportions of AD prescriptions are described through a 5-year comparison of annual cross-sections of patients prescribed ADs between 2009 and 2014. Analyses were performed using SAS version 9.4.

Ethics

The CPCSSN received ethics approval from the research ethics boards of all host Universities for all participating networks and from the Health Canada Research Ethics Boards. The present study received ethics approval from the McGill University Faculty of Medicine Institutional Research Board.

Results

Population characteristics

Table 1 provides description of characteristics of diabetic patients prescribed ADs in 2014 (n=10,152), stratified by sex. This sample is described according to age, BMI, presence of co-morbidities and anti-diabetic medication prescription. In the cohort of diabetic patients prescribed ADs in 2014, more of the patients were female than male. Among those with BMI measurements (n=7,387; 27.2% missing), almost all were overweight and nearly two thirds were obese (BMI>30 kg/m^2). History of depression was identified in over half of the sample. With regard to other comorbidities, hypertension was most frequent, followed by osteoarthritis and COPD. Regarding prescription of anti-diabetic medication, most were prescribed oral medications, followed by a combination of oral medications and insulin, and less than 10% were prescribed insulin alone. In over ¼ of the diabetic patients, no prescription of diabetes medications was identified.

Characteristics of males and females in the sample were generally comparable, with a few exceptions. Mean age and mean BMI (group mean of the individuals' median values) were comparable between the sexes. Males were only slightly older than females, and slightly more females were obese than males. Very slight differences in diabetes medication prescription were observed, with more males than females prescribed insulin (either alone or in combination with oral medications).

Antidepressant prescription

Table 2 presents the frequency and proportion of ADs prescribed for the 2014 cross-section of diabetic patients, in terms of pharmacological class and individual medication, stratified by sex and history of depression. The most frequently prescribed AD classes given to people with diabetes were SSRI, followed by SNRI, TCA, SARI, NDRI, NaSSA and MAOI. A trend was observed in which the prescription of certain ADs for patients with a history of depression differed from those without. For diabetics with a history of depression, the most commonly prescribed classes were SSRI, followed by SNRI, TCA, SARI, NDRI and NaSSA. The most frequently prescribed classes of AD given to diabetic patients without depression were TCAs, followed by SSRIs, SNRIs, SARIs, NDRI and NaSSA.

The most frequently prescribed AD agents given to diabetic patients with a history of depression were Citalopram, Escitalopram, Venlafaxine, Trazodone, Bupropion, Amitriptyline and Sertraline. For diabetic patients without a history of depression, the most frequently prescribed ADs were Amitriptyline, Trazodone, Venlafaxine, Nortriptyline, Duloxetine, Citalopram and Bupropion.

In people with diabetes and a history of depression, more females than males were prescribed ADs in general. The proportion with which individual ADs were prescribed were generally comparable between the sexes, with a few exceptions. Amitriptyline and Venlafaxine were more often prescribed for females than males, and Mirtazapine was more often prescribed for males than females.

For diabetic patients without a history of depression, larger differences were observed. The prescription frequency was higher for females than males for each of the individual SSRIs;

Amitriptyline, Nortriptyline and Venlafaxine were more frequently prescribed in females than males; and Bupropion was more prescribed for males than females.

Table 3 provides a comparison of 5 annual cross-sections of diabetic patients prescribed ADs between 2009 and 2014. Across the 5-year span, the relative proportions with which the pharmacological classes were prescribed remained stable. Changes in proportions were observed for individual medications within the classes, however. Increases in relative prescription frequency was observed for Escitalopram, Duloxetine, Bupropion, Mirtazapine and Trazodone. A decrease was observed for Citalopram, Paroxetine, Venlafaxine and Amitriptyline.

Discussion

Interpretation

The present study provides a description of AD prescription in Canada for people with diabetes. This appears to be the first epidemiological study of primary care practices describing the prescription of ADs for people with diabetes in Canada. Additionally, very few studies to date have described the prescription of ADs in terms of individual medication.

This study's findings regarding the proportion with which the different classes of ADs were prescribed for people with diabetes and a history of depression are consistent with other research using CPCSSN data but described the prescription of ADs in a Canadian primary care population with a history of depression (with and without diabetes) (88). The finding that SSRIs are most frequently prescribed class of AD is consistent with literature suggesting SSRIs are the "drugs of choice for the treatment of depressive disorders" (124). Evidence from clinical trials suggests SSRIs and NDRIs may be associated with improved glucose metabolism (19, 34, 38) and that TCAs and SNRIs may be associated with impaired glucose metabolism (20, 32, 33). The present study shows that almost half of diabetics prescribed ADs were given SNRIs or TCAs.

While evidence so far is inconclusive, the frequency with which these ADs are prescribed may be cause for concern as it appears that primary healthcare providers are not aware of the negative impact of these medications with regard to glucose metabolism. Given the similarity in prescription patterns for the general primary care population with a history of depression (88) and diabetic patients with a history of depression, it appears that healthcare providers' AD prescription choices are not affected by current evidence regarding the risks certain ADs pose for people with diabetes.

This study found that over half of the diabetic patients prescribed ADs had a history of depression. *History of depression* was used to define those for whom ADs were prescribed for the treatment of depression. The prescription of ADs for people with depression tended to differ from those without. This is to be expected as ADs are prescribed for a number of other conditions than depression, including: general anxiety or panic disorders, obsessive-compulsive disorder, and eating disorders; and clinically accepted off-label indications include insomnia, tobacco-cessation, headaches, neuropathic pain and chronic pain (85). In patients without a history of depression (and those with a history of depression but were prescribed an AD for the treatment of another condition), the ADs were more likely prescribed for other conditions. The trend of differing prescription frequencies between males and females for specific ADs is largely related to the frequency with which these conditions are presented and treated in primary care.

Between 2009 and 2014, an increase in AD prescription frequency was observed; however, this may be a reflection of gradual increases participating clinics as well as their data capture. Increases in relative prescription frequency were observed for newer ADs Trazodone, Bupropion and Mirtazapine, for which little research on their effect on glycemic control has been published. Citalopram and Paroxetine (SSRIs) decreased in frequency, while Escitalopram, an

alternate SSRI, increased; and Duloxetine (SNRI) decreased while Venlafaxine, an alternate SNRI, increased. A slight decrease in prescription frequency was observed for Amitriptyline (TCA), relative to an increase in the prescription of Nortriptyline, an alternate TCA. Despite growing evidence that TCAs are associated with impaired glucose metabolism, no change in proportional frequency was observed over the course of the five-year observation period.

Limitations

One limitation is that the sample is only somewhat representative of the general Canadian population. In comparison with 2011 Canadian census data, the CPCSSN population in 2013 over-represented older adults and under-represented younger adults; and the CPCSSN population comprised significantly fewer young adult males than the general Canadian population (125). Furthermore, given that the practices participating in the CPCSSN were not randomly selected, the population may not be generalizable to the Canadian primary care population (125). Participating practices tended to be those affiliated with the practice-based research networks involved in the project and those more engaged in chronic disease surveillance. Nevertheless, the trends observed with this sample are expected to compare to those in a wider population. Future research should seek to confirm this hypothesis.

Second, the case detection algorithms for depression has a relatively high false positive rate. The case definition for depression detects *lifetime depression*, and includes manic disorders and bipolar mood disorders. Lifetime depression was used in this study to approximate the prescription of ADs for the treatment of depression as AD dose and reason for prescription were not consistently recorded or could not be coded. As patients with a history of depression may be

given ADs for other conditions, the number of ADs prescribed to people with depression over-estimates those given ADs for the treatment of depression.

A third limitation of this study pertains to the use of health records for research. While primary care EMRs permit the naturalistic examination of prescriptions and health conditions over time, some values may be missing (not entered or could not be coded) and some fields may differ between EMR products or may not be used in a standardized manner by primary healthcare providers. Were the data available, AD dose, referral to psychotherapy and diagnoses for other health conditions for which ADs are prescribed would have been included to better describe depression treatment practices in primary care patients living with diabetes.

The present research study provides information on the prescription of ADs for people with diabetes in Canada. This information is valuable as it provides insight into the implications of research evaluating the impact of ADs on glycemic control in people with diabetes. As new and more conclusive evidence on the effects of ADs on blood sugar emerges, or as new clinical recommendations are introduced, this study provides the means of estimating the number of patients that will be affected.

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Canada on behalf of 9 practice-based research networks associated with departments of family medicine across Canada. The views expressed herein do not necessarily represent the views of the PHAC.

Table 1. Characteristics of adult patients with diabetes mellitus prescribed an antidepressant in 2014 (October 1st 2013 to September 20th 2014)

	Male (n=3920, 38.6%) n (%)	Female (n=6232, 61.4%) n (%)	Total (N=10152) n (%)
Age - mean (sd)	63.3 (13.10)	62.7 (14.60)	63.0 (14.03)
18-35	96 (2.5)	288 (4.6)	384 (3.8)
36-55	945 (24.2)	1531 (24.7)	2476 (24.5)
>55	2861 (73.3)	4384 (70.7)	7245 (71.7)
BMI – mean* (sd)	32.5 (6.59)	33.9 (7.89)	33.4 (7.44)
Underweight (<18.5)	4 (0.1)	13 (0.3)	17 (0.2)
Normal (18.5-24.9)	259 (9.0)	484 (10.7)	743 (10.1)
Overweight (25-29.9)	846 (29.5)	1053 (23.3)	1899 (25.7)
Obese (>30.0)	1764 (61.4)	2964 (65.7)	4728 (64.0)
Multimorbidity			
No comorbidity**	619 (15.8)	815 (13.1)	1434 (14.1)
Hypertension	2241 (57.2)	3529 (56.6)	5770 (56.8)
Depression	2044 (52.1)	3661 (58.8)	5705 (56.2)
COPD	649 (16.6)	865 (13.9)	1514 (14.9)
Osteoarthritis	942 (24.0)	1997 (32.0)	2939 (29.0)
Antidiabetic medication classes			
No diabetes medication	1014 (25.9)	1744 (28.0)	2758 (27.2)
Insulin only	276 (7.0)	408 (6.5)	684 (6.7)
Oral medication only	1907 (48.7)	3025 (48.5)	4932 (48.6)
Both oral and insulin	723 (18.4)	1055 (16.9)	1778 (17.5)

* Group mean of individuals' median BMI values

** None of the conditions for which CPCSSN case definitions were developed

Table 2. Number and proportion of patients prescribed antidepressants in 2014 (October 1st 2013 to September 30th 2014) by pharmacological class and agent, stratified by history of depression and sex

	History of depression (n=5705)		No history of depression (n=4447)		Total (n=10152)
	Male (n=2044) n (%)	Female (n=3661) n (%)	Male (n=1876) n (%)	Female (n=2571) n (%)	n (%)
Tricyclics antipderessants	**219 (10.7)**	**561 (15.3)**	**675 (36.0)**	**965 (37.5)**	**2420 (23.8)**
Amitriptyline	145 (7.1)	386 (10.5)	440 (23.5)	672 (26.1)	1643 (16.2)
Nortriptyline	60 (2.9)	120 (3.3)	199 (10.6)	216 (8.4)	595 (5.9)
Doxepin	6 (0.3)	29 (0.8)	20 (1.1)	45 (1.8)	100 (1.0)
Imipramine	3 (0.2)	15 (0.4)	12 (0.6)	25 (1.0)	55 (0.5)
Desipramine	3 (0.2)	5 (0.1)	9 (0.5)	10 (0.4)	27 (0.3)
Trimipramine	2 (0.1)	9 (0.2)	4 (0.2)	6 (0.2)	21 (0.2)
Clomipramine	8 (0.4)	5 (0.1)	4 (0.2)	4 (0.2)	21 (0.2)
Amoxapine	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Maprotiline	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Selective serotonin reuptake inhibitors	**1236 (60.5)**	**2209 (60.3)**	**473 (25.2)**	**768 (29.9)**	**4686 (46.2)**
Citalopram	473 (23.1)	852 (23.3)	142 (7.6)	222 (8.6)	1689 (16.6)
Escitalopram	363 (17.8)	588 (16.1)	115 (6.1)	188 (7.3)	1254 (12.4)
Sertraline	208 (10.2)	408 (11.1)	63 (3.4)	110 (4.3)	789 (7.8)
Paroxetine	104 (5.1)	215 (5.9)	127 (6.8)	202 (7.9)	648 (6.4)
Fluoxetine	96 (5.0)	176 (4.8)	26 (1.4)	66 (2.6)	364 (3.6)
Fluvoxamine	32 (1.6)	41 (1.1)	9 (0.5)	8 (0.3)	90 (0.9)
Serotonin antagonist reuptake inhibitors	**262 (12.8)**	**425 (11.6)**	**344 (18.3)**	**412 (16.0)**	**1443 (14.2)**
Trazodone	262 (12.8)	425 (11.6)	344 (18.3)	412 (16.0)	1443 (14.2)
Serotonin-norepinephrine reuptake inhibitors	**442 (21.6)**	**948 (25.9)**	**405 (21.6)**	**667 (25.9)**	**2462 (24.3)**
Venlafaxine	289 (14.1)	641 (17.5)	234 (12.5)	427 (16.6)	1591 (15.7)
Duloxetine	141 (6.9)	289 (7.9)	159 (8.5)	225 (8.8)	814 (8.0)
Desvenlafaxine	24 (1.2)	46 (1.3)	13 (0.7)	23 (0.9)	106 (1.0)
Monoamine oxidase inhibitors	**7 (0.3)**	**6 (0.2)**	**1 (0.1)**	**4 (0.2)**	**18 (0.2)**
Phenelzine	0 (0)	1 (0.0)	1 (0.1)	0 (0.0)	2 (0.0)
Tranylcypromine	1 (0.1)	2 (0.1)	0 (0.0)	0 (0.0)	3 (0.0)
Moclobemide	6 (0.3)	3 (0.1)	0 (0.0)	4 (0.0)	13 (0.1)
Norepinephrine-dopamine reuptake inhibitors	**244 (11.9)**	**375 (10.2)**	**171 (9.1)**	**145 (5.6)**	**935 (9.2)**
Bupropion	244 (11.9)	375 (10.2)	171 (9.1)	145 (5.6)	935 (9.2)
Norepinephrine and specific serotonergic antidepressants	**207 (10.1)**	**290 (7.9)**	**60 (3.2)**	**65 (2.5)**	**622 (6.1)**
Mirtazapine	207 (10.1)	290 (7.9)	60 (3.2)	65 (2.5)	622 (6.1)

Table 3. Number and proportion of patients prescribed antidepressants by pharmacological class and agent– 5-year comparison (2009-2014)

	2009-2010 (n=6474) n (%)	2010-2011 (n=7590) n (%)	2011-2012 (n=8501) n (%)	2012-2013 (n=9368) n (%)	2013-2014 (n=10152) n (%)
Tricyclic antidepressants	**1540 (23.8)**	**1774 (23.4)**	**1876 (22.1)**	**2225 (23.8)**	**2420 (23.8)**
Amitriptyline	1129 (17.4)	1281 (16.9)	1319 (15.5)	1487 (15.9)	1643 (16.2)
Nortriptyline	286 (4.4)	344 (4.5)	388 (4.6)	564 (6.0)	595 (5.9)
Doxepin	75 (1.2)	73 (1.0)	79 (0.9)	81 (0.9)	100 (1.0)
Imipramine	48 (0.7)	50 (0.7)	62 (0.7)	53 (0.6)	55 (0.5)
Desipramine	22 (0.3)	17 (0.2)	15 (0.2)	27 (0.3)	27 (0.3)
Trimipramine	27 (0.4)	23 (0.3)	18 (0.2)	21 (0.2)	21 (0.2)
Clomipramine	18 (0.3)	19 (0.3)	24 (0.3)	21 (0.2)	21 (0.2)
Amoxapine	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Maprotiline	2 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Selective serotonin reuptake inhibitors	**3062 (47.3)**	**3689 (48.6)**	**4096 (48.2)**	**4362 (46.6)**	**4686 (46.2)**
Citalopram	1407 (21.7)	1627 (21.4)	1664 (21.4)	1662 (17.7)	1689 (16.6)
Escitalopram	457 (7.1)	654 (8.6)	943 (11.1)	1086 (11.6)	1254 (12.4)
Sertraline	388 (6.0)	502 (6.6)	603 (7.1)	690 (7.4)	789 (7.8)
Paroxetine	560 (8.6)	626 (8.6)	640 (7.5)	652 (7.0)	648 (6.4)
Fluoxetine	272 (4.2)	312 (4.1)	324 (3.8)	330 (3.5)	364 (3.6)
Fluvoxamine	69 (1.1)	79 (1.0)	77 (0.9)	82 (0.9)	90 (0.9)
Serotonin antagonist reuptake inhibitors	**775 (12.0)**	**893 (11.8)**	**1093 (12.9)**	**1300 (13.9)**	**1443 (14.2)**
Trazodone	775 (12.0)	893 (11.8)	1093 (12.9)	1300 (13.9)	1443 (14.2)
Serotonin-norepinephrine reuptake inhibitors	**1515 (23.4)**	**1706 (22.5)**	**2056 (24.2)**	**2244 (24.0)**	**2462 (24.3)**
Venlafaxine	1209 (18.7)	1285 (16.9)	1464 (17.2)	1520 (16.2)	1591 (15.7)
Duloxetine	304 (4.7)	396 (5.2)	551 (6.5)	687 (7.3)	814 (8.0)
Desvenlafaxine	40 (0.6)	72 (0.9)	94 (1.1)	90 (1.0)	106 (1.0)
Monoamine oxidase inhibitors	**10 (0.2)**	**15 (0.2)**	**12 (0.1)**	**18 (0.2)**	**18 (0.2)**
Phenelzine	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	2 (0.0)
Tranylcypromine	1 (0.0)	3 (0.0)	2 (0.0)	4 (0.0)	3 (0.0)
Moclobemide	8 (0.1)	12 (0.2)	10 (0.1)	13 (0.1)	13 (0.1)
Norepinephrine-dopamine reuptake inhibitors	**619 (6.9)**	**703 (9.3)**	**828 (9.7)**	**866 (9.2)**	**935 (9.2)**
Bupropion	619 (6.9)	703 (9.3)	828 (9.7)	866 (9.2)	935 (9.2)
Norepinephrine and specific serotonergic antidepressants	**302 (4.7)**	**363 (4.8)**	**452 (5.3)**	**561 (6.0)**	**622 (6.1)**
Mirtazapine	302 (4.7)	363 (4.8)	452 (5.3)	561 (6.0)	622 (6.1)

PREFACE TO MANUSCRIPT 2

This article, intended for publication in BMJ, provides an estimate of the impact of antidepressant medications on glycemic control. This objective was achieved through computation of generalized linear mixed models estimating the mean HbA1c ratios of diabetic patients prescribed Amitriptyline, Venlafaxine, Trazodone and Escitalopram relative to Citalopram in people with diabetes mellitus. The data were obtained from primary care electronic medical records data collected by the Canadian Primary Care Sentinel Surveillance Network (CPCSSN) in 2014.

MANUSCRIPT ABSTRACT

Context: Depression is a common comorbidity in people with diabetes mellitus (DM) that is associated with increased risk of poor glycemic control. Evidence suggests that, independent of depression, certain antidepressant medications (AD) further increase this risk. Few observational studies have examined the impact of individual ADs on glycemic control in people with DM. The objective of this study was to measure the impact of Citalopram, Amitriptyline, Venlafaxine, Trazodone and Escitalopram (the ADs most frequently prescribed in Canada for people with DM) on glycated hemoglobin (HbA1c) in Canadian primary care patients with DM.

Methods: A retrospective cohort study of electronic medical records (EMR) from 115 primary care practices across Canada was undertaken. Data were obtained from the Canadian Primary Care Sentinel Surveillance Network (CPCSSN). The sample population comprised 1084 diabetic patients with 1127 prescriptions of either Citalopram, Amitriptyline, Venlafaxine, Trazodone, or Escitalopram and with baseline and post-exposure HbA1c measurements. Generalized linear mixed models were computed to estimate the mean HbA1c ratios for patients given latter 4 ADs as percentages relative to Citalopram.

Results: Mean HbA1c ratios for Amitriptyline, Venlafaxine, Trazodone and Escitalopram were lower than Citalopram, however results were not statistically significant. Sensitivity analyses, which examined the impact of ADs on HbA1c over different periods of exposure found lowest mean HbA1c ratios for patients prescribed Trazodone (0.97; 95% CI: 0.92 to 1.02) and Escitalopram (0.97; 95% CI: 0.92 to 1.03).

Discussion: The results of this cohort study of Canadian primary care practices suggest that Citalopram, the AD most prescribed for diabetic patients, may be less effective than

Trazodone and Escitalopram in people with DM. Future research should seek to distinguish the impact of depression severity and weight, and examine the dose-effect relationship over time. In addition, more knowledge is needed on the physiological mechanisms explaining the relationship between certain ADs and changes in glucose metabolism. Until more conclusive evidence is available, diabetic patients should be monitored more closely when prescribed ADs.

THE IMPACT OF ANTIDEPRESSANT THERAPY ON GLYCEMIC CONTROL IN CANADIAN PRIMARY CARE PATIENTS WITH DIABETES MELLITUS

Justin Gagnon, Marie-Thérèse Lussier, Brenda MacGibbon, Stella S. Daskalopoulou, Gillian Bartlett

Introduction

Depression is a common comorbidity in people with diabetes mellitus, which increases the risk of poor health outcomes (6, 10, 12, 13). People with diabetes and depression are at greater risk of poor diabetes control, diabetes-related complications, multimorbidity and mortality compared with those with either condition alone (4-9). The relationship between diabetes and depression is bidirectional. Depression is associated with a decline in self-management behaviours (11, 23) as well as pathophysiology linked to impaired glucose metabolism (96), and people with diabetes are at increased risk of depression (14). While treatment of depression is expected to break this cycle, evidence suggests that some antidepressant medications (AD) directly and indirectly interfere with normal glucose metabolism (19).

ADs are most often prescribed in primary care (126). The pharmacological classes of ADs most commonly prescribed in Canadian primary care are: selective serotonin reuptake inhibitors (SSRI); serotonin-norepinephrine reuptake inhibitors (SNRI), tricyclic antidepressants (TCA), serotonin antagonist reuptake inhibitors (SARI), norepinephrine-dopamine reuptake inhibitors (NDRI), noradrenergic and specific serotonergic antidepressants (NaSSA) (88). Citalopram (SSRI), Amitriptyline (TCA), Venlafaxine (SNRI), Trazodone (SARI) and

Escitalopram (SSRI) were identified as the most frequently prescribed ADs for people with diabetes in Canada, according to a recent pan-Canadian study of primary care practices (127).

Research has linked Citalopram with improved glucose metabolism (34, 35) and weight loss (35), which can reduce the risk of poor glycemic control. The other 4 medications have not been studied as extensively. While the effects of Amitriptyline on glucose metabolism are inconclusive (128), it has been associated with weight gain (26), which can cause insulin resistance and poor diabetes control (129). Other TCAs (i.e. Imipramine) have been associated with impaired glucose control (33). The results of trials examining the impact of Venlafaxine are also inconclusive (26); however Duloxetine, another SNRI, has been linked to weight loss (32). Less is known about the impact of Trazodone (SARI) on glycemic control. Escitalopram has not been studied as extensively, but other SSRIs are generally associated with improved glucose metabolism (36, 37, 39) and weight loss (115). The volume of research on particular ADs is disproportional to the frequency with which they are prescribed, as more evidence exists for some of the less commonly prescribed ADs. Moreover, the findings of trials in this field are inconsistent, due in large part to the heterogeneity of study designs and sample populations.

Most observational studies have focused on the association between AD use overall, or grouped by pharmacological class, and diabetes onset. A number of epidemiological studies have reported an association between AD use in general and increased risk of diabetes onset (49-51, 53, 117). With regard to the pharmacological classes, SSRIs, TCAs and SNRIs have been associated with increased risk of diabetes onset, with TCAs (47) and concurrent use of SSRIs and TCAs (54) being associated with the greatest increase in risk. ADs within the same class may differ in terms of their impact on glucose metabolism (107), therefore ADs should be examined individually. However, epidemiological research has seldom examined the impact of

individual ADs. Given the need for more epidemiological research in this area, the purpose of this study is to estimate the impact of Citalopram, Amitriptyline, Venlafaxine, Trazodone, and Escitalopram on glycemic control in Canadian primary care patients with diabetes.

Methods

Data source and study population

This is a retrospective cohort study of electronic medical records (EMR) from primary care providers across Canada. Data were obtained from the Canadian Primary Care Sentinel Surveillance Network (CPCSSN). The CPCSSN database was developed for chronic disease surveillance and research. The CPCSSN is somewhat representative of the general Canadian population, however older adults are over-represented and young adult males are under-represented (125). EMR data from 115 primary care practices in 9 Canadian provinces and 1 territory were extracted, anonymized, cleaned and coded by the CPCSSN in September 2014. Included in the study were diabetic patients who were prescribed either Citalopram, Amitriptyline, Venlafaxine, Trazodone, and Escitalopram; and had at least one baseline and post-exposure HbA1c measure (n=1084). Figure 1 provides an illustration of the sample selection, which is described in greater detail below.

Diabetes mellitus

Diabetes mellitus (identified in 66,617 patients at the moment of extraction) was identified using the validated (121) CPCSSN case detection algorithm (Appendix I), which identifies cases using a combination of patients' health problem list, medication prescription

records, laboratory results and billing information. The case definition includes type 1 diabetes (T1DM) and type 2 diabetes (T2DM). A recent validity test obtained a sensitivity of 95.6 (93.4-97.9), a specificity of 97.1 (96.3-97.9), a positive predictive value of 87.0 (83.5-90.5), and a negative predictive value of 99.1 (98.6-99.6) compared to detailed chart review conducted by the primary healthcare provider (121). The case definition has an excellent negative predictive value with a slight tendency to include false positives.

Antidepressant medications (exposure)

Among patients with diabetes, 20,419 had a record of an AD prescription. Anatomical Therapeutic Chemical (ATC) codes were assigned to all medications in patient health records. Medications listed under *antidepressants* by the World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology (69) were included. ADs were classified according to their corresponding pharmacological class, according to the Compendium of Pharmaceuticals and Specialties (CPS) (85).

Series of AD prescriptions (separated by 15 days or less) were joined to define periods of continuous use. Exclusion criteria consisted of: concurrent prescriptions of different ADs; AD prescription periods occurring within 1 year of one another (washout); and prescriptions lasting less than 90 days.

From the diabetic patients with distinct and continuous AD prescription periods (n=3512), the sample was limited to those prescribed either Citalopram, Amitriptyline, Venlafaxine, Trazodone, and Escitalopram. The indication of prescription was not consistently reported, therefore, all AD prescriptions regardless of indication were considered. Medication

dose was also not available. History of depression, included as a covariable, was used to define ADs prescribed for the treatment of depression.

Glycated hemoglobin (outcome)

Glycated hemoglobin (HbA1c) is a measure of the mean glucose concentration approximately over the previous 12 weeks, reflecting the 90-120-day lifespan of red blood cells. The Canadian Diabetes Association (CDA) recommends targeting below 7.0% (or 53.0 mmol/mol) in people with diabetes, to reduce the risk of complications (64). From the patients prescribed 1 of the 5 selected ADs, those with baseline and post-exposure (post AD prescription) measures were selected. The HbA1c measurement closest to the AD prescription start date (*Time 0*) and no more than 12 months prior was used as the *baseline* value. Post-exposure HbA1c values were all HbA1c measurements taken within 18 months after *Time 0*, or until the medication was stopped. While HbA1c approximates the mean glucose concentration of the 3 previous months, the first 3 months were included to detect possible short-term effects of ADs, which were assessed using sensitivity analyses. *Exposure duration* was defined as the number of days from *Time 0* when post-exposure HbA1c was measured.

Covariables

The following variables were included in the analyses: baseline HbA1c, age, sex, body mass index (BMI), diabetes medication type, history of depression, as well as presence of hypertension, osteoarthritis and chronic obstructive pulmonary disease (COPD). Age at the moment of data extraction was computed using the patients' dates of birth. A median BMI was

computed for each of the patients using all recorded BMI values, when available. The median was selected as the reliability of BMI values was suspect and the median reduced the influence of potential outliers. Diabetes medication type comprised 4 categories: no medication; oral anti-diabetic medication; oral medications and insulin; and insulin. The health conditions included in the analyses (history of depression, hypertension, osteoarthritis and COPD) were identified by using validated CPCSSN (121) case definitions that combine patients' health problem list, medication prescription records, billing and laboratory results (when applicable). The case definition for history of depression (Appendix I) includes depressive disorders as well as bipolar and manic mood disorders. The definition was found to have a sensitivity of 81.1 (77.2–85.0) and a specificity of 94.8 (93.7–95.9) compared with detailed chart review by the primary healthcare provider (121). The case definition for depression has an excellent negative predictive value with a moderate tendency to include false positives.

Statistical Analyses

Patient characteristics (Table 4), stratified by the 5 ADs, were described using frequencies and proportions and means and standard deviations, as appropriate. ANOVA was used to test for differences between AD groups for continuous variables (age and BMI), and Chi-Square tests were used for categorical variables (depression, hypertension, osteoarthritis, COPD and diabetes medication type). If a significant difference was found in the latter cases, specific differences between groups were examined using factorial logistic regression. Baseline and post-exposure HbA1c measures (Table 5) were described using means and standard deviations, and ANOVA was used to test for differences.

A generalized linear mixed (GLM) model (130) was computed in order to estimate the impact of ADs on repeated HbA1c measures. GLM models are ideal for longitudinal data with non-normally distributed dependent variables (which is often the case with health data) as they permit modeling of random and/or fixed error terms at the level of clusters (within subjects) and the whole (between subjects) (130). Analyses were clustered at the level of individual patient-prescription periods. The logarithmic link function was used. The impact of ADs on HbA1c computed using the GLM model was represented in terms of mean ratios for Amitriptyline, Venlafaxine, Trazodone and Escitalopram relative to Citalopram, the most frequently prescribed of these ADs. The reference category for diabetes medication type was *no diabetes medication*. Model fitness was assessed for inclusion of hypertension, osteoarthritis and COPD as covariables using the Akaike Information Criterion (AIC).

An initial model (Table 6) was computed which included all patients prescribed 1 of the 5 ADs. BMI was not included in this initial model as this variable contained a number of missing values (27.4% of patients had no BMI measurements). Sensitivity analyses were performed to account for BMI and history of depression. A sub-model that included only patients with BMI measurements (Table 7) was computed, followed by a subsequent sub-model including only those with a history of depression (Table 8). Furthermore, sensitivity analyses were performed to estimate the impact of ADs for specific periods of exposure. Four additional sub-models were computed for each of the 3 models described above in which post-exposure HbA1c measurements were divided into periods of exposure: 0 to 3 months; 3 to 6 months; 6 to 12 months; and 12 to 18 months.

Power calculations

A total of 1084 patients were fulfilled all the eligibility criteria and included in the analyses. Analyses were performed at the level of *patient prescription-periods* (prescriptions of longer than 90 days and separated by a 12-month washout period) of which there were 1127. Using an F-test MANOVA using a sample size of 505 (5 times the smallest group – Escitalopram; n=101), α of 0.05, power of 0.8 and 5 groups, the required effect size was estimated at 2.4% (using G*Power version 3.1). The analyses were performed using SAS version 9.4.

Ethics

CPCSSN received ethics approval from the research ethics boards of all host Universities for all participating networks and from the Health Canada Research Ethics Boards. The present study received ethics approval from the McGill University Faculty of Medicine Research Board.

Results

Population characteristics

A total of 1084 patients with 1127 prescription-periods were included in the GLM models analyses. Table 4 presents the characteristics of the population, stratified by the prescribed AD. Citalopram was most frequently prescribed (29.3%), followed by Amitriptyline (27.6%), Venlafaxine (17.4%), Trazodone (16.7%) and Escitalopram (9.0%). The groups differed significantly according to age (ANOVA), sex, history of depression and osteoarthritis (Chi-Square). The patients given Escitalopram were significantly younger than those prescribed

Trazodone (mean difference=-7.90; 95%CI=-12.44 to -3.35), Citalopram (mean difference=-5.70; 95%CI=-9.89 to -1.51) and Amitriptyline (mean difference=-5.61; 95%CI=-9.89 to -1.39), and those prescribed Venlafaxine were significantly younger than those prescribed Trazodone (mean difference=-5.12; 95%CI=-8.89 to -1.35). A significantly lower proportion of females were prescribed Trazodone than Venlafaxine (OR=0.49; 95%CI=0.32 to 0.74) and Citalopram (OR=0.68; 95%CI=0.47 to 0.98). Additionally, AD groups differed significantly according to history of depression; the greatest proportion of patients with a history of depression were on Citalopram and Escitalopram (76.9% and 70.7%, respectively). A significantly smaller proportion of patients given Citalopram or Venlafaxine had osteoarthritis compared to the other 3 ADs. No significant differences were found between AD groups for BMI, hypertension, COPD and diabetes medication type.

HbA1c measurements

Table 5 provides a comparison of mean change in HbA1c following AD exposure from baseline for patients prescribed Citalopram, Amitriptyline, Venlafaxine, Trazodone or Escitalopram. Change in HbA1c was reported in terms of the mean of all post-exposure measures, as well as in terms of specific periods of exposure (0 to 3 months; 3 to 6 months; 6 to 12 months; 12 to 18 months) in order to examine changes in HbA1c values over the course of AD treatment. At baseline, HbA1c values of patients prescribed Citalopram were significantly more elevated than those prescribed Venlafaxine (mean difference=0.26; 95%CI=0.02 to 0.49) and Trazodone (mean difference=0.39; 95%CI=0.15 to 0.63). No significant differences in post-exposure HbA1c change relative to baseline were found between ADs. The largest decrease in HbA1c post-exposure was observed between 3 and 6 months following AD exposure in the

group prescribed Escitalopram (-0.29; sd=0.90); and the largest increases were observed between 6 and 12 months in the group prescribed Amitriptyline (0.21; sd=1.28), and between 12 and 18 months in the group prescribed Venlafaxine (0.21; sd=0.91).

Impact of antidepressants on HbA1c

The results of the GLM model for the full sample population (n=1127) are presented in Table 6. The table also presents the results of sub-models computed for specific periods of exposure to the ADs (0 to 3 months; 3 to 6 months; 6 to 12 months; and 12 to 18 months). The table shows that mean HbA1c was lower for the 4 ADs compared to Citalopram (as the mean ratios were all less than 1.00). The 95% confidence intervals all crossed the line of unity, suggesting no statistically significant difference was detected, however the confidence intervals all included the minimum detectable effect (2.4%). Trazodone had the lowest proportion relative to Citalopram at 97.0%. The sensitivity analyses examining the impact of ADs on HbA1c for different periods of exposure showed that between 6 and 12 months after AD exposure, Trazodone and Escitalopram had the lowest proportional means compared to Citalopram.

Table 7 provides the results of the model that includes adjustment for BMI using the subset of patients with BMI measurements (n=811). Like the previous model, mean HbA1c was lower for the 4 ADs compared to Citalopram. In the sub-models which distinguished different periods of exposure, the mean HbA1c ratios were higher for all ADs compared to Citalopram between 3 and 6 months of exposure. The highest proportional mean was observed in the group prescribed Amitriptyline (102.2%). After 6 months of exposure, the mean HbA1c ratios for all ADs were lower than Citalopram. Again, as in the previous model, the lowest mean ratios were observed for Escitalopram and Trazodone after 6 months of exposure.

Table 8 provides the results of the model computed using patients diabetes, a history of depression and BMI measurements (n=404). The results of this model show relatively comparable mean HbA1c ratios for the 4 ADs. The confidence intervals all crossed the line of unity and were relatively wide compared to the previous two tables. As with the previous tables, the smallest mean ratios were observed for the group prescribed Escitalopram and Trazodone after 6 months.

With regard to the covariables, use of insulin and combined oral diabetes mediation and insulin were associated with a statistically significant increase in mean HbA1c relative to no diabetes medication, whereby the confidence intervals included the line of unity as well as the minimum detectable effect. In those with a history of depression, the mean HbA1c was lower than those without, with only a slight intersection of the confidence intervals with the line of unity. The mean HbA1c ratio for those with a history of depression was lower than those without, however no significant difference was detected. Age and duration of exposure appeared to have no significant effect on HbA1c.

Discussion

This study estimated the effect of Amitriptyline, Venlafaxine, Trazodone and Escitalopram on HbA1c compared to Citalopram for patients with DM using a large Canadian primary care EMR database. Although significant differences in HbA1c could not be detected, as the confidence intervals for the mean HbA1c ratios crossed the line of unity, the confidence intervals included the minimum detectable effect. While the null hypothesis could not be rejected, the possibility of Amitriptyline, Venlafaxine, Trazodone and Escitalopram being associated with lower mean HbA1c values is not dismissed. Sensitivity analyses comparing

periods of exposure (>6 months) suggest that Trazodone and Escitalopram may be more effective than Citalopram for prolonged use. Lower mean HbA1c ratios for Trazodone and Escitalopram were also observed in the sub-model controlling for BMI as well as the model computed for the subset of patients with a history of depression. Future research should seek to confirm these findings in a larger sample of patients specifically prescribed these ADs for the treatment of depression, and whose disease course is comparable (or at least measured and included in the analyses).

Mean HbA1c ratios at baseline, as well as ratios within the first 6 months of AD exposure were relatively comparable. This suggests that, if these ADs do indeed directly impact glucose metabolism, this effect takes time (at least 3 months). Given that HbA1c is a measure that estimates the average glucose concentration of the previous 90 to 120 days (64), no observable effect was expected within this time frame, unless the ADs drastically modified glucose metabolism in such a short time. It appears, therefore, that the ADs did not have a drastic, immediate effect.

The finding that HbA1c was significantly higher among people taking insulin (insulin alone and in combination with oral diabetes medications) compared to no diabetes medication suggests that those needing to administer insulin to regulate glucose (T1DM and insulin-dependent T2DM) generally had poorer glycemic control (131). The lower mean HbA1c ratio observed for patients with a history of depression was contrary to what was expected, given that depression is generally associated with poorer glycemic control (6). This finding might suggest increased consultation frequency, and thus closer monitoring, among patients with depression, which is consistent with the literature (132).

Some limitations of the present study must be considered. The CPCSSN database consists of medical data, entered by healthcare providers for clinical purposes. While this real-world medical data is extremely valuable for observational research, the data were derived from multiple healthcare providers using diverse EMR products. While the lack of standardization of EMR fields and data entry can affect the availability and reliability of the data, the CPCSSN has performed a great amount of cleaning and coding, which provides standardization and vastly improves the reliability of the medical data for use in research. What remains an issue, however, are fields that are not consistently used by healthcare providers and fields that have not yet been coded sufficiently. Other studies have recommended including the following variables, which could not be included in this study: smoking status, alcohol consumption, dyslipidemia, referral to a psychotherapist or combined cognitive and pharmacological depression treatment, indication for AD prescription, severity of depression and AD dose. AD dose, especially, would have permitted an estimation of a dose-response relationship between the ADs and HbA1c, which has been observed in other research (133). The HbA1c estimates may have been mediated by AD dose, which is linked to the indication for which the AD was prescribed (124). As patients may have been prescribed ADs for other indications than depression, use of *history of depression* (to approximate patients actively suffering from depression) over estimates those prescribed ADs for the treatment of depression. Inclusion of indication for AD prescription and severity of depression could have accounted for differences in illness between patients. Mixed effects modeling accounts for a certain degree of within-subject variation over time, as well as between-subject variation, accounting partly for unmeasured covariables; however, as that not all patients were equally exposed to depression, the effect of depression and the AD could not be separated. Also due to inconsistent availability of dose information, changes in diabetes medications also

was not included as a covariable. As diabetes medications may have been adjusted to counter increases in glucose levels resulting from depression or AD use, the hyperglycemic effects of certain ADs may be underestimated. Finally, time varying weight (or BMI) were not included as factors since the dataset contained a number of potentially erroneous BMI values, which affected the reliability of all values. Multiple imputation for the missing values was not considered as healthcare providers may be more likely weigh patients with extensive health problems and/or excessive weight, therefore the missing values were considered non-random.

Another limitation is that the findings may not be generalizable to all patients with diabetes prescribed ADs, given the over-representation of older adults and under-representation of young adult men in the CPCSSN population (125). The CPCSSN data are obtained from primary care practices participating in the project. Participating primary care providers are slightly more likely to be those interested in chronic disease surveillance and use of EMRs. Despite limited generalizability to the Canadian population or to all Canadian primary care practices, the internal validity is not compromised.

Evidence on the impact of ADs and knowledge about the mechanisms linking certain ADs with impaired glucose metabolism is currently inconclusive. The results of observational studies often do not corroborate the findings of clinical trials (20-22, 134). Studies in this field are relatively heterogeneous in terms of population and study design, making their synthesis in meta-analyses difficult. This research makes a distinct contribution by highlighting the change in HbA1c associated with ADs at specific time intervals. It also uses robust statistical analyses for modeling changes in HbA1c, which accounts for baseline HbA1c for each individual, and individual-level variation in HbA1c over time, as well as between-individual variations. The use

of random effects models is ideal for clinical data as it accounts for within- and between-subject variation over time, and allows for valid inferences to be made about the effect of ADs.

Conclusion

Certain ADs could be metabolically unfavorable for people with diabetes. The present study is one of few cohort studies using clinical data and examining the impact of individual ADs on HbA1c. The findings of this research contribute important evidence towards the risks certain ADs may pose to people with diabetes mellitus. GLM modeling found lower mean HbA1c ratios for Amitriptyline, Venlafaxine, Trazodone and Escitalopram compared to Citalopram, however the results were not statistically significant.Sensitivity analyses suggested that Escitalopram and Trazodone may be more effective than Citalopram, in terms of their impact on glucose metabolism, especially after 6 months of use. Future research should seek to confirm these findings, and account for changes in weight and DM medication over time and estimate the dose-response relationship between ADs and HbA1c.

The CDA recommends closer monitoring for people with diabetes taking antipsychotic medications, but not antidepressants (64). Despite the need for more solid evidence, current guidelines should draw attention to the possible risk ADs may pose for people with diabetes and recommend closer monitoring.

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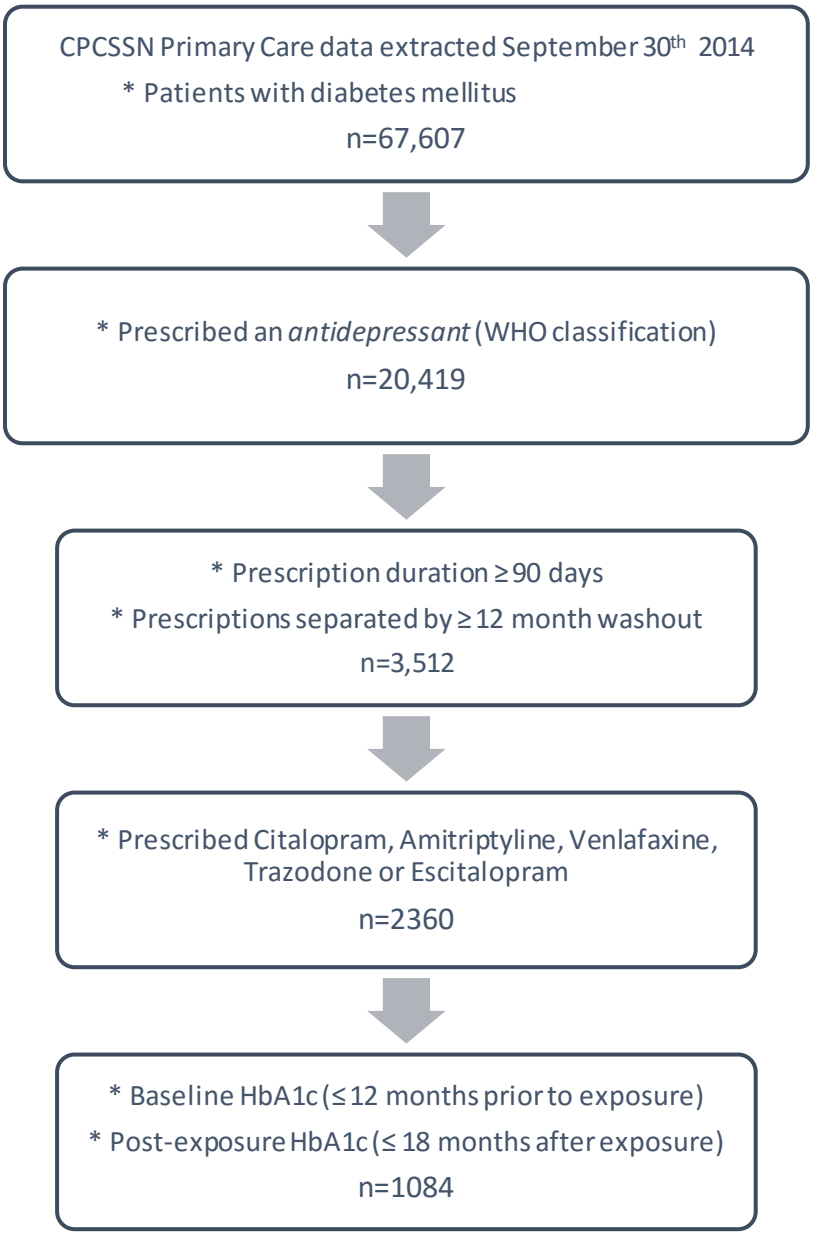

Figure 1. Illustration of study sample selection

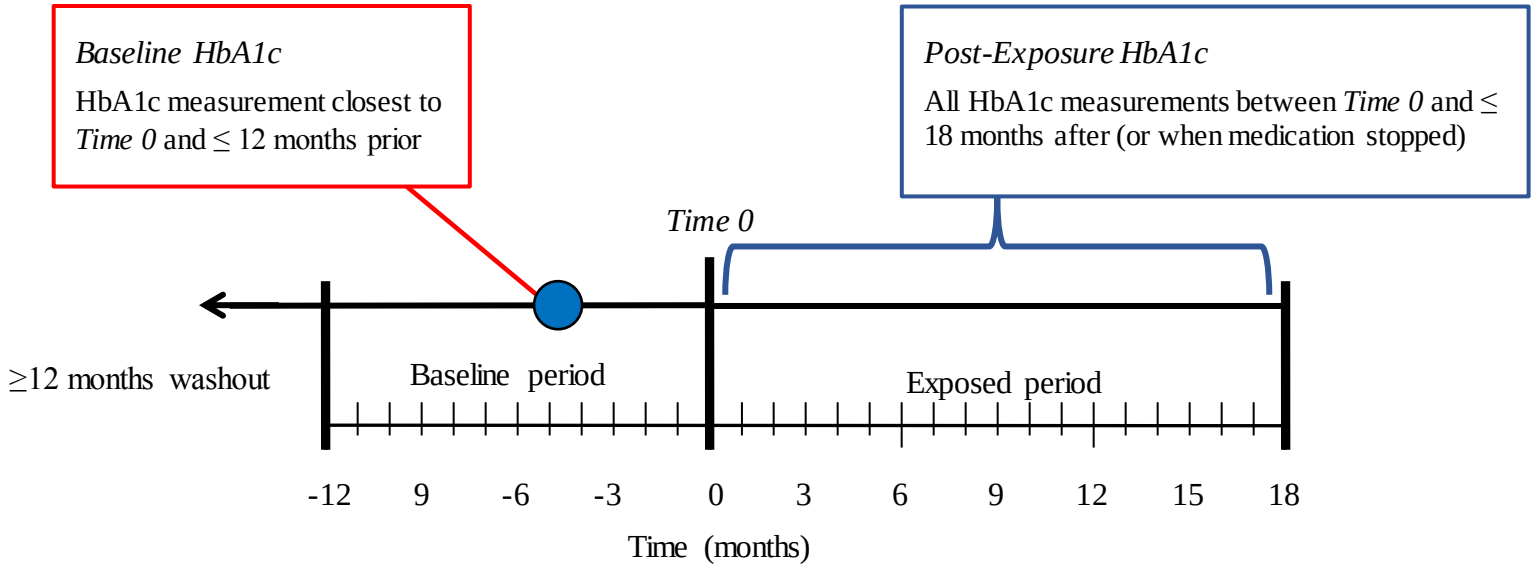

Figure 2. Illustration of baseline and exposed blood sugar measures

Table 4. Characteristics of diabetic patients prescribed Citalopram, Amitriptyline, Venlafaxine, Trazodone or Escitalopram stratified by antidepressant agent

	Citalopram n=320 (29.3%) n (%)	Amitriptyline n=302 (27.6%) n (%)	Venlafaxine n=190 (17.4%) n (%)	Trazodone n=183 (16.7%) n (%)	Escitalopram n=99 (9.0%) n (%)	Total n=1094* (100%) n (%)
Age - mean(sd)	67.6 (13.8)	67.5 (11.1)	64.7 (12.2)	69.8 (14.1)	61.9 (14.4)	67 (13.1)
Sex (women)	186 (58.1)	172 (57)	125 (65.8)	89 (48.6)	57 (57.6)	629 (57.5)
BMI - mean(sd) n=787	31.9 (6.5)	33 (6.8)	32.8 (6.7)	31.5 (6.9)	33.9 (7.6)	32.5 (6.8)
Underweight (<18.5)	1 (0.5)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.1)
Normal (18.5-24.9)	28 (12.7)	28 (12.6)	17 (12.4)	20 (15)	7 (9.3)	100 (12.7)
Overweight (25-29.9)	61 (27.7)	55 (24.8)	36 (26.3)	40 (30.1)	22 (29.3)	214 (27.2)
Obese (>=30)	130 (59.1)	139 (62.6)	84 (61.3)	73 (54.9)	46 (61.3)	472 (60)
Depression	246 (76.9)	59 (19.5)	106 (55.8)	57 (31.1)	70 (70.7)	538 (49.6)
Antidiabetic Rx						
Insulin and oral Rx	85 (26.6)	89 (29.5)	52 (27.4)	47 (25.7)	20 (20.2)	293 (26.8)
Insulin only	17 (5.3)	23 (7.6)	17 (8.9)	10 (5.5)	11 (11.1)	78 (7.1)
Oral Rx only	168 (52.5)	145 (48)	95 (50)	97 (53)	49 (49.5)	554 (50.6)
No diabetes Rx	50 (15.6)	45 (14.9)	26 (13.7)	29 (15.8)	19 (19.2)	169 (15.4)
Hypertension	217 (67.8)	199 (65.9)	128 (67.4)	124 (67.8)	58 (67.8)	726 (66.4)
Osteoarthritis	89 (27.8)	115 (38.1)	49 (25.8)	79 (43.2)	39 (39.4)	371 (33.9)
COPD	58 (18.1)	50 (18.1)	20 (10.5)	29 (18.9)	10 (10.1)	167 (15.3)

* 10 patients were included in more than one column as they were prescribed different antidepressants on separate occasions. The means and proportions in the Total column were computed for the 1084 patients.

Table 5. Mean change in HbA1c from baseline stratified by antidepressant agent

	Citalopram n=333 mean (sd)	Amitriptyline n=312 mean (sd)	Venlafaxine n=195 mean (sd)	Trazodone n=186 mean (sd)	Escitalopram n=101 mean (sd)	Total n=1127 mean (sd)
Baseline HbA1c	**7.4 (1.5)**	**7.2 (1.4)**	**7.1 (1.3)**	**7.2 (1.4)**	**7.4 (1.9)**	**7.2 (1.5)**
Post-exposure Δ from baseline	**-0.01 (1.5)**	**0.06 (1.14)**	**0.06 (0.95)**	**-0.07 (0.97)**	**-0.17 (0.87)**	**0.001 (1.08)**
0 to 3 months	-0.16 (0.73)	-0.05 (1.05)	-0.05 (0.73)	-0.19 (0.93)	-0.25 (0.92)	-0.12 (0.88)
3 to 6 months	-0.21 (0.87)	-0.03 (0.97)	-0.04 (1.03)	-0.08 (1.03)	-0.29 (0.90)	-0.11 (0.96)
6 to 12 months	0.14 (1.51)	0.21 (1.28)	0.14 (1.07)	0.03 (1.03)	-0.08 (0.82)	0.13 (1.13)
12 to 18 months	0.19 (1.34)	0.09 (1.20)	0.21 (0.91)	0.01 (0.80)	0.06 (0.77)	0.13 (1.13)

Table 6. Model predicting the association between antidepressants and mean HbA1c ratio in people with diabetes

	Full model n=1127		0 to 3 months n=624		3 to 6 months n=551		6 to 12 months n=546		12 to 18 months n=309	
	Mean HbA1c ratio	95% CI	Mean HbA1c ratio	95% CI	Mean HbA1c ratio	95% CI	Mean HbA1c ratio	95% CI	Mean HbA1c ratio	95% CI
Baseline HbA1c	1.079	1.068 to 1.091	1.09	1.071 to 1.109	1.082	1.056 to 1.109	1.067	1.046 to 1.089	1.069	1.039 to 1.101
Antidepressants (reference: Citalopram)										
Amitriptyline	**0.988**	**0.947 to 1.031**	1.010	0.928 to 1.100	1.006	0.922 to 1.098	0.966	0.896 to 1.041	0.968	0.872 to 1.073
Venlafaxine	**0.979**	**0.936 to 1.024**	0.994	0.909 to 1.086	1.000	0.912 to 1.097	0.962	0.888 to 1.042	0.963	0.866 to 1.069
Trazodone	**0.970**	**0.923 to 1.018**	0.990	0.900 to 1.088	0.993	0.900 to 1.095	0.954	0.875 to 1.040	0.935	0.824 to 1.062
Escitalopram	**0.971**	**0.916 to 1.030**	0.993	0.898 to 1.097	0.994	0.873 to 1.133	0.928	0.836 to 1.031	0.973	0.821 to 1.152
Exposure duration (days)	1.000	1.000 to 1.000	1.000	0.999 to 1.001	1.000	0.999 to 1.001	1.000	0.999 to 1.000	1.000	0.999 to 1.001
Characteristics										
Age	0.999	0.998 to 1.000	1.000	0.997 to 1.002	0.999	0.997 to 1.001	0.998	0.996 to 1.000	0.999	0.996 to 1.002
Sex (female)	1.015	0.985 to 1.045	1.014	0.958 to 1.074	1.012	0.952 to 1.075	1.023	0.971 to 1.079	1.004	0.930 to 1.084
History of depression	0.976	0.943 to 1.010	1.005	0.941 to 1.072	0.975	0.909 to 1.046	0.954	0.899 to 1.013	0.966	0.886 to 1.053
Antidiabetic medication type (reference: no diabetes medication)										
Insulin and oral Rx	1.075	1.02 to 1.133	1.035	0.939 to 1.141	1.067	0.96 to 1.187	1.108	1.004 to 1.223	1.094	0.957 to 1.249
Insulin only	1.093	1.022 to 1.168	1.042	0.916 to 1.186	1.099	0.964 to 1.255	1.118	0.989 to 1.263	1.124	0.952 to 1.327
Oral Rx only	1.010	0.962 to 1.060	0.994	0.91 to 1.087	1.016	0.923 to 1.118	1.007	0.920 to 1.103	1.024	0.904 to 1.160

Table 7. Model predicting the association between antidepressants and change in HbA1c in diabetics, adjusting for body mass index

	Full model n=811		0 to 3 months n=445		3 to 6 months n=406		6 to 12 months n=398		12 to 18 months n=232	
	Mean HbA1c ratio	95% CI	Mean HbA1c ratio	95% CI	Mean HbA1c ratio	95% CI	Mean HbA1c ratio	95% CI	Mean HbA1c ratio	95% CI
Baseline HbA1c	1.080	1.066 to 1.093	1.093	1.07 to 1.116	1.080	1.05 to 1.111	1.069	1.045 to 1.094	1.069	1.033 to 1.105
Antidepressants (reference: Citalopram)										
Amitriptyline	**0.986**	**0.939 to 1.035**	1.015	0.919 to 1.121	1.022	0.925 to 1.130	0.958	0.88 to 1.043	0.951	0.849 to 1.065
Venlafaxine	**0.984**	**0.933 to 1.038**	1.004	0.902 to 1.117	1.005	0.903 to 1.118	0.958	0.87 to 1.056	0.981	0.867 to 1.11
Trazodone	**0.971**	**0.918 to 1.027**	0.995	0.891 to 1.111	1.016	0.906 to 1.139	0.948	0.861 to 1.044	0.920	0.797 to 1.062
Escitalopram	**0.975**	**0.909 to 1.046**	0.995	0.883 to 1.121	1.018	0.868 to 1.193	0.942	0.829 to 1.07	0.944	0.769 to 1.158
Exposure duration (days)	1.000	1.000 to 1.000	1.000	0.999 to 1.001	1.000	0.998 to 1.001	1.000	0.999 to 1.001	1.000	0.999 to 1.001
Characteristics										
Age	0.999	0.997 to 1.000	0.999	0.997 to 1.002	0.999	0.996 to 1.002	0.998	0.995 to 1.000	0.998	0.995 to 1.002
Sex (Women)	1.009	0.975 to 1.045	1.008	0.941 to 1.079	1.017	0.946 to 1.094	1.011	0.95 to 1.075	0.996	0.912 to 1.087
Body Mass Index	0.998	0.995 to 1.000	0.999	0.994 to 1.004	0.998	0.993 to 1.004	0.997	0.992 to 1.001	0.996	0.989 to 1.002
Depression	0.974	0.937 to 1.012	1.000	0.928 to 1.079	0.983	0.908 to 1.064	0.949	0.887 to 1.015	0.966	0.877 to 1.062
Antidiabetic medication type (reference: no diabetes medication)										
Insulin and oral Rx	1.113	1.041 to 1.189	1.064	0.945 to 1.198	1.093	0.954 to 1.253	1.159	1.018 to 1.319	1.140	0.962 to 1.351
Insulin only	1.118	1.023 to 1.221	1.051	0.888 to 1.244	1.117	0.931 to 1.339	1.150	0.97 to 1.365	1.172	0.957 to 1.437
Oral Rx only	1.023	0.962 to 1.087	1.003	0.899 to 1.119	1.024	0.905 to 1.158	1.028	0.911 to 1.16	1.044	0.892 to 1.222

Table 8. Model predicting the association between antidepressants and change in HbA1c in diabetics with a history of depression, adjusting for body mass index

	Full model n=404		0 to 3 months n=227		3 to 6 months n=196		6 to 12 months n=194		12 to 18 months n=117	
	Mean HbA1c ratio	95% CI	Mean HbA1c ratio	95% CI	Mean HbA1c ratio	95% CI	Mean HbA1c ratio	95% CI	Mean HbA1c ratio	95% CI
Baseline HbA1c	1.078	1.060 to 1.096	1.088	1.059 to 1.118	1.073	1.032 to 1.116	1.067	1.035 to 1.100	1.076	1.021 to 1.133
Antidepressants (reference: Citalopram)										
Amitriptyline	**1.008**	**0.935 to 1.087**	1.027	0.888 to 1.188	1.038	0.890 to 1.209	0.984	0.860 to 1.126	0.977	0.798 to 1.195
Venlafaxine	**0.991**	**0.926 to 1.061**	1.008	0.879 to 1.156	0.983	0.855 to 1.129	0.979	0.861 to 1.114	0.992	0.848 to 1.160
Trazodone	**0.981**	**0.898 to 1.073**	1.014	0.852 to 1.206	0.986	0.809 to 1.201	0.982	0.847 to 1.137	0.919	0.705 to 1.199
Escitalopram	**0.985**	**0.908 to 1.068**	1.001	0.871 to 1.151	1.040	0.867 to 1.247	0.946	0.815 to 1.098	0.951	0.743 to 1.218
Exposure duration (days)	1.000	1.000 to 1.000	1.000	0.998 to 1.002	1.000	0.997 to 1.002	1.000	0.999 to 1.001	1.000	0.999 to 1.001
Characteristics										
Age	1.000	0.998 to 1.002	1.000	0.996 to 1.004	1.000	0.996 to 1.004	0.999	0.995 to 1.003	0.999	0.994 to 1.005
Sex (Women)	1.003	0.953 to 1.056	1.017	0.922 to 1.121	0.989	0.888 to 1.101	1.017	0.926 to 1.118	0.975	0.854 to 1.112
BMI	1.000	0.996 to 1.004	1.000	0.993 to 1.008	1.001	0.993 to 1.009	0.999	0.992 to 1.006	0.999	0.989 to 1.009
Antidiabetic medication type (reference: no diabetes medication)										
Insulin and oral Rx	1.122	1.015 to 1.241	1.095	0.906 to 1.323	1.090	0.884 to 1.345	1.159	0.962 to 1.396	1.161	0.901 to 1.496
Insulin only	1.129	0.989 to 1.290	1.081	0.838 to 1.394	1.092	0.832 to 1.434	1.196	0.936 to 1.529	1.158	0.839 to 1.599
Oral Rx only	1.029	0.938 to 1.128	1.032	0.866 to 1.229	1.019	0.847 to 1.226	1.032	0.872 to 1.222	1.048	0.830 to 1.322

THESIS DISCUSSION

This research sought to describe AD medication prescription practices in Canada for people with diabetes and then measure the impact of the 5 most frequently prescribed ADs on glycemic control. These aims were achieved through statistical analysis of Canadian primary care EMR data. The most commonly prescribed ADs for Canadian primary care patients with diabetes mellitus were Citalopram (SSRI), Amitriptyline (TCA), Venlafaxine (SNRI), Trazodone (SARI), and Escitalopram (SSRI). The generalized linear mixed effects modeling found lower mean HbA1c values for Amitriptyline, Venlafaxine, Trazodone and Escitalopram compared to Citalopram, the most frequently prescribed AD. The lowest mean HbA1c ratios relative to Citalopram were observed in patients prescribed Trazodone and Escitalopram after 6 months of AD use, suggesting these two may be less unfavorable than Citalopram after prolonged AD use. These results, however, were not statistically significant but give an indication of areas for future investigation.

The findings of this research are generally consistent with current evidence but also provide greater precision with regard to potential differences between specific agents. Prior research has found an association between Citalopram and hypoglycemia (34, 35), and in some cases weight loss (35), which can improve glucose metabolism. Escitalopram has been less extensively studied, but other SSRIs, with the exception of Paroxetine (39), have had similar results (34, 36, 115). There is a lack of research comparing their effects. The present research project suggests Escitalopram may be preferable for people with diabetes. Amitriptyline has been associated with weight gain (26) and other TCAs have been associated with short-term increases in fasting glucose (33). This study did not find a significant difference between Citalopram and Amitriptyline. Venlafaxine has not generally been associated with hyperglycemia or change in

weight (26), however research has associated Duloxetine, another SNRI, with increased fasting glucose (32). This research found no significant difference between Venlafaxine and Citalopram. Research on the impact of Trazodone on glucose metabolism has been scant. The present research suggests Trazodone may pose less risk of hyperglycemia than Citalopram in people with diabetes.

Numerous studies examining the effects of one medication on blood sugar have generalized their findings to its pharmacological class. However, the binding profiles between ADs can differ greatly, which can produce a range of effects that alter glucose metabolism (107). Hypotheses involving the physiological mechanisms of ADs have been proposed to explain current evidence regarding the hyperglycemic effects of certain ADs. In a study which proposes a novel approach to the classification of ADs, Derijks et al. (2008) compare the binding profiles of 20 common ADs according to 2 transporters (5-HT serotonin reuptake transporter and NE norepinephrine reuptake transporter) and 4 receptors (muscarine M_3 receptor, histamine H_1, α_1-receptor and 5-HT_{2C}-receptor) (107). They report that Amitriptyline has affinity for all the transporters and receptors; Escitalopram has specific affinity for the 5-HT serotonin transporter; Citalopram has a slight affinity for the H_1 histamine receptor in addition to the 5-HT serotonin transporter[1]; Trazodone has affinity mainly for the alpha α_1-receptor and very slight affinity for the 5-HT_{2C} receptor; and Venlafaxine has strong affinity for the 5-HT transporter and slight affinity for the NE transporter and 5-HT_{2C} receptor (136). Another study by Derijks et al. (2008) involving spontaneous reports that hyperglycemia was most pronounced for ADs with affinity

[1] The Citalopram and Escitalopram molecules are virtually the same, however Citalopram comprises 2 citalopram enantiomers (S and R isomers) and Escitalopram comprises only the S enantiomer 135. Sanchez C, Bogeso KP, Ebert B, Reines EH, Braestrup C. Escitalopram versus citalopram: the surprising role of the R-enantiomer. Psychopharmacology. 2004;174(2):163-76..

for norepinephrine transporter, 5-HT_{2C} receptor and H_1 receptor (137). This finding is concurrent with the present research, which suggests Trazodone and Escitalopram (which have negligible affinity for these receptors and transporter) are least unfavorable.

Research has proposed physiological links between these binding sites and hyperglycemia. First, the norepinephrine transporter appears to directly stimulate glycogenolysis and gluconeogenesis, and reduce glucose uptake and glucose usage, which results in increased glucose levels (138). Researchers posit that the 5-HT_{2C} and H_1 receptors stimulate food cravings thereby increasing risk of weight gain, which can in turn reduce insulin sensitivity and increase glucose levels (139).

In addition to the physiological links between ADs and glucose metabolism, the observed differences may be attributed to the differences in the indications for which the ADs were prescribed. The presentation of certain symptoms related to depression, such as anxiety, low mood or low energy, can have an influence on which ADs are prescribed. As suggested by this research, Citalopram, Escitalopram and to a slightly lesser extent Venlafaxine are more commonly prescribed for the treatment of depression. Indications for Escitalopram and Venlafaxine approved by Health Canada also include anxiety disorders (85). As Trazodone has pronounced sedative effects, it is more often considered a second-line treatment of depression. Other unapproved indications for this medication include insomnia and acute agitation (85). History of depression was least frequent in diabetic patients given Amitriptyline. Indications for this medication include neuropathic pain, which is common in people with more severe advanced cases of diabetes mellitus (85). The course of a patient suffering from depression characterized by low energy differs that of a patient suffering from depression characterized by anxiety, and these differ greatly from the courses of patients suffering from insomnia or chronic pain. Low

energy and chronic pain may hinder physical activity, but may differ in terms of physiopathology affecting glucose levels. Insomnia is linked to chronic stress and circadian rhythm disruption (140), which can impact glucose metabolism as well as feeding behaviours (141-143). The multiple conditions for which ADs are prescribed involve different physiopathology and have different impacts on self-care behaviours. The influence of these factors could not be assessed in the present research.

Current Canadian Diabetes Association guidelines pertaining to the treatment of depression in people with diabetes recommend prescribing ADs only for the treatment of acute depression and to prevent recurrence of depression (64). They also recommend integration of psychosocial interventions in care plans; however, these are commonly inaccessible or unaffordable. Regular metabolic monitoring is also recommended, but only for people treated with antipsychotic medications. No specific recommendations for closer monitoring are provided for ADs in general. Given the risks ADs pay pose for people with diabetes, however, these recommendations should err on the side of caution and include all ADs, until evidence is more conclusive about which medications pose little or no risk.

THESIS SUMMARY AND CONCLUSIONS

This research provided a description of AD prescription for people with diabetes mellitus in Canada. It also contributes important evidence towards the risks certain ADs may pose to people with diabetes mellitus. The results of this research suggest that Citalopram, currently the most frequently prescribed AD, may not be the least unfavorable AD. While results were not statistically significant, this research found lower mean HbA1c values for Trazodone and Escitalopram compared to Citalopram after prolonged use. This research is one of very few

epidemiological studies examining the impact of individual ADs on glycemic control and employs robust statistical methods in the analysis of longitudinal health data.

Future research should seek to corroborate these findings in a larger population with comorbid diabetes and depression. Research should aim to control for AD prescription indications, use of psychotherapy in conjunction with AD therapy, and time-varying factors such as changes weight, changes in diabetes medication and AD dose. It should also aim to disentangle the effect of depression and the independent effects of ADs and further examine the potential mechanisms of ADs that explain their impact on glucose metabolism.

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APPENDICES

Appendix I: The Canadian Primary Care Sentinel Surveillance Network (CPCSSN)

The Canadian Primary Care Sentinel Surveillance Network (CPCSSN) collects and stores patient information from electronic medical records (EMR) from primary care providers across Canada for chronic disease surveillance and research purposes. The CPCSSN is a network of 11 practice-based research networks (PBRN) across 9 Canadian provinces and 1 territory. It extracts, anonymizes, cleans and codes health data on 5 chronic diseases and 3 neurological conditions: hypertension, diabetes, depression, osteoarthritis, chronic obstructive pulmonary disease (COPD), epilepsy, Parkinson's disease and dementia. Validated case definitions have been developed by the CPCSSN for each of these conditions.

Practice-based research networks (PBRN)

The CPCSSN comprises 11 practice-based research networks:

- British Columbia Primary Care Research Network (BCPCReN): British Columbia
- Southern Alberta Primary Care Research Network (SAPCReN): Alberta, Northwest Territories
- Northern Alberta Primary Care Research Network (NAPCReN): Alberta
- Manitoba Primary Care Research Network (MaPCReN): Manitoba
- Delivery Primary Healtcare Information (DELPHI) Project: Ontario
- University of Toronto Practice Based Research Network (UTOPIAN): Ontario
- Eastern Ontario Network (EON): Ontario
- CPCSSN@MAC: Ontario
- Réseau de recherche en soins primaires de l'Université de Montréal (RRSPUM) : Quebec
- Maritime Family Practice Research Network (MaRNet-FP): Nova Scotia, New-Brunswick, Prince Edward Island
- Atlantic Practice Based Research Network (APBRN): Newfoundland and Labrador

Chronic disease case definitions

The CPCSSN developed and validated (121) case definitions for the 8 chronic conditions under their study. The following tables are a reproduction of the CPCSSN disease definitions for diabetes and depression (144).

Diabetes

Text-based Definition

A CPCSSN diagnosis of diabetes includes diabetes mellitus type 1 and type 2, controlled or uncontrolled. Gestational diabetes, chemically induced (secondary) diabetes, or neonatal diabetes are not included as well as polycystic ovarian syndrome and hyperglycemia. The definition does not include pre-diabetes or similar states or conditions such as impaired fasting glucose or glucose intolerance.

Operational Definition

Diabetes Mellitus (Occurrences of any of the following indicators is enough to index the disease.)

Billing	OR	Problem List	OR	Medication	OR	Lab Result
Minimum Two occurrences of the following codes within two years: 1. 250, Diabetes mellitus		Any occurrence of the following codes: 1. 250, Diabetes mellitus		DrugName — ATC Code ACARBOSE — A10BF01 GLIBENCLAMIDE — A10BB01 GLICLAZIDE — A10BB09 GLIMEPIRIDE — A10BB12 INSULIN (HUMAN) — A10AB01 INSULIN (HUMAN) — A10AC01 INSULIN (HUMAN) — A10AD01 INSULIN (HUMAN) — A10AE01 INSULIN ASPART — A10AB05 INSULIN ASPART — A10AD05 INSULIN DETEMIR — A10AE05 INSULIN GLARGINE — A10AE04 INSULIN LISPRO — A10AB04 INSULIN LISPRO — A10AD04 METFORMIN — A10BA02 METFORMIN AND ROSIGLITAZONE — A10BD03 SITAGLIPTIN — A10BH01 TOLBUTAMIDE — A10BB03 INSULIN (PORK) — A10AC03 The following diagnosis if exist in patient's problem list make **the medication criteria alone insufficient**: • 256.4, Polycystic Ovarian Syndrome • 648.8, Gestational Diabetes • 249, Secondary (chemical induced) Diabetes • 790.29, Hyperglycemia NOS • 775.1, Neonatal diabetes mellitus		1. Any HbA1C >= 7 2. Two occurrences within one year of Fasting Glucose >7

Depression

Text-based Definition

A CPCSSN diagnosis of depression includes episodic mood disorders or a depressive disorder not elsewhere classified, it includes bipolar, manic affective disorder, manic episodes as well as mild depression (not just "clinical depression"). It does not include anxiety disorders, alcohol or drug induced mental disorders, schizophrenic disorders, delusional disorders, other non-organic psychoses, pervasive developmental disorders, or other intellectual disabilities.

Operational Definition

Depression						
Billing	**OR**	**Problem List**	**OR**	**Medication**	**OR**	**Lab Result**
Any occurrence of the following codes: 1. 296, Episodic mood disorders 2. 311, Depressive disorder not elsewhere classified		Any occurrence of the following codes: 1. 296, Episodic mood disorders 2. 311, Depressive disorder not elsewhere classified		AMITRIPTYLINE AND PSYCHOLEPTICS N06CA01 CITALOPRAM N06AB04 ESCITALOPRAM N06AB10 FLUOXETINE N06AB03 FLUVOXAMINE N06AB08 MIRTAZAPINE N06AX11 MOCLOBEMIDE N06AG02 SERTRALINE N06AB06 TRANYLCYPROMINE N06AF04 The following diagnosis if exist in patient's problem list make **the medication criteria alone insufficient**: • 300, Anxiety disorders		**N/A**