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Anuja Azad Sharma Date

Classes of antidepressant medications and associations with type 2 diabetes: a systematic review

By

Anuja Azad Sharma
Master of Public Health

Hubert Department of Global Health

_____

Lisa Staimez, Ph.D.
Committee Chair

Classes of antidepressant medications and associations with type 2 diabetes: a systematic review

By
Anuja Azad Sharma

Thesis Committee Chair: Lisa Staimez, PhD

An abstract of a thesis submitted to the Faculty of the Rollins School of Public Health of Emory University in partial fulfillment of the requirements for the degree of Master of Public Health in Global Health
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Abstract

Classes of antidepressant medications and associations with type 2 diabetes: a systematic review

By: Anuja Azad Sharma

Introduction: Antidepressant use has increased over recent years. Some studies suggest that antidepressants may affect glucose metabolism and that the associations of antidepressants to glucose metabolism may be modified by class of drug. Our aim was to systematically assess specific classes of antidepressant medication for potential variation in longitudinal risk of type 2 diabetes.

Methods: A systematic literature search for longitudinal studies examining antidepressant classes was conducted on PubMed. Our search was restricted to papers published from 1990 to 2018 and only included studies assessing the incidence of new-onset diabetes or changes in blood glucose, HbA1c or insulin levels in adult subjects with unipolar depression treated with antidepressants. Our search was restricted to English language studies having a sample size ≥ 30.

Results: Eight studies published between 2007 and 2016 met our inclusion criteria. Research designs included 4 cohort studies, 3 case-control studies and 1 case series. A significant increase in risk of developing type 2 diabetes was reported across medication classes (Selective Serotonin Reuptake Inhibitor: 3/7, Tricyclic antidepressant: 3/6, concurrent use of Selective Serotonin Reuptake Inhibitor and Tricyclic antidepressant: 1/1, Serotonin and Norepinephrine Reuptake Inhibitor: 1/1 and Tetracyclic antidepressant: 1/1).

Conclusion: Longitudinal evidence from the past 25 years suggests that antidepressant class may impact glucose dysregulation and the risk of developing type 2 diabetes differentially. Given the possible heterogeneity of different antidepressants on the association with blood glucose levels, we suggest future studies classify the risk of type 2 diabetes according to antidepressant class, dosage, and duration of use. Future studies that formally evaluate the risks and benefits of prescribing specific antidepressants should include potential impacts of diabetes risk.

Classes of antidepressant medications and associations with type 2 diabetes: a systematic review

By
Anuja Azad Sharma

Thesis Committee Chair: Lisa Staimez, PhD

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"A hundred times every day I remind myself that my inner and outer life depend on the labors of other men, living and dead, and that I must exert myself in order to give in the measure as I have received and am still receiving."

- Albert Einstein

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List of Abbreviations:

ADM	Antidepressant Medication
T2DM	Type 2 diabetes mellitus
SSRI	Selective Serotonin Reuptake Inhibitor
TCA	Tricyclic Antidepressant
SNRI	Serotonin Norepinephrine Reuptake Inhibitor
MAO	Monoamine oxidase inhibitor
WHO	World Health Organization

Chapter I: Review of Literature

Non-communicable diseases (NCDs)

NCDs are diseases that cannot be transmitted from one individual to another [1]. Key examples of NCDs are cancer, diabetes, respiratory diseases and cardiovascular diseases [1]. NCDs are leading cause of death worldwide. In 2018, NCDs were responsible for 41 million deaths or 71% of total deaths globally [2]. NCDs tend to affect people for a long time leading to increased spending on healthcare thereby becoming a huge economic burden on the affected individuals and their families [3]. WHO predicts that by year 2035, the global cost of NCDs will exceed 45 trillion dollars, a price higher than any other group of diseases [3]. Many NCD control initiatives have been made by public health organizations around the world yet the number of people affected by NCDs only keeps rising [4]. A critical component shockingly absent from NCD control initiatives is mental health [5].

Mental Health and NCDs

Many NCDs are a result of poor lifestyle choices which in turn are heavily impacted by mental health [5]. The behavioral risk factors for NCDs like smoking, alcohol consumptions, substance abuse, sedentary lifestyle, weight gain, etc. are often a symptom of mental health disorders [5]. Lack of mental health care among people affected with NCDs often increases the morbidity and mortality rates which is believed to be a critical reason behind NCD control initiative's lack of success [5]. This realization prompted the World Health Organization to launch the Noncommunicable Disease and Mental Health Division (NMH) in 2018 [6].

Type 2 diabetes mellitus (T2DM) and Depression: Bidirectional Relationship

T2DM and depression are an excellent example of how mental health and NCD interact with each other. Type 2 diabetes mellitus (T2DM) is one of the most common and rapidly growing non-communicable disease worldwide that has affected more than 450 million people globally [7].

T2DM affects the way glucose is metabolized in the body. Individuals affected with T2DM either resists the effects of insulin, a peptide hormone secreted by pancreas that regulates glucose levels circulating in the blood stream or cannot produce enough of it [8]. Main symptoms of T2DM include increased thirst, frequent urination, increased appetite, fatigue, weight fluctuations, blurred vision and poor wound healing [8].

Depression is the most common mental health disorder affecting more than 300 million worldwide [9]. It is the leading cause of disability worldwide and a major contributor of overall global burden of disease [9]. Depression is characterized by persistently depressed mood or loss of interest in activities causing significant impairment in daily life [10]. Depression can be long-lasting and at its worst, can lead to suicide [10]. Depression results from a complex interaction of social, psychological and biological factors and can lead to a range of behavioral and physical symptoms [10].

Both T2DM and depression share a bidirectional relationship in a way that one can course the other. Individuals with depression have 37% increased risk of developing T2DM, and people with T2DM are twice as likely to have depression than those without [11,12]. A recent meta-analysis of 11 studies including nearly 50,000 people with type 2 diabetes but without depression at baseline has indicated that the incidence of depression is 24% higher in people with diabetes [13]. A meta-

analysis of 9 cohort studies found that adults with depression had a 37 % increased risk of developing type 2 diabetes after accounting for factors common to both disorders including sex, body mass index, and poverty [14].

Mechanisms underlying the bidirectional relationship

A number of mechanisms have been suggested to explain the link between diabetes and depression. These mechanisms include shared inflammatory pathways, dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis, common metabolic effectors like leptin, in addition to a host of environmental, genetic, and behavioral factors. Figure 1 shows the shared biological changes that occur in diabetes and depression that may increase the risk of the other condition [29].

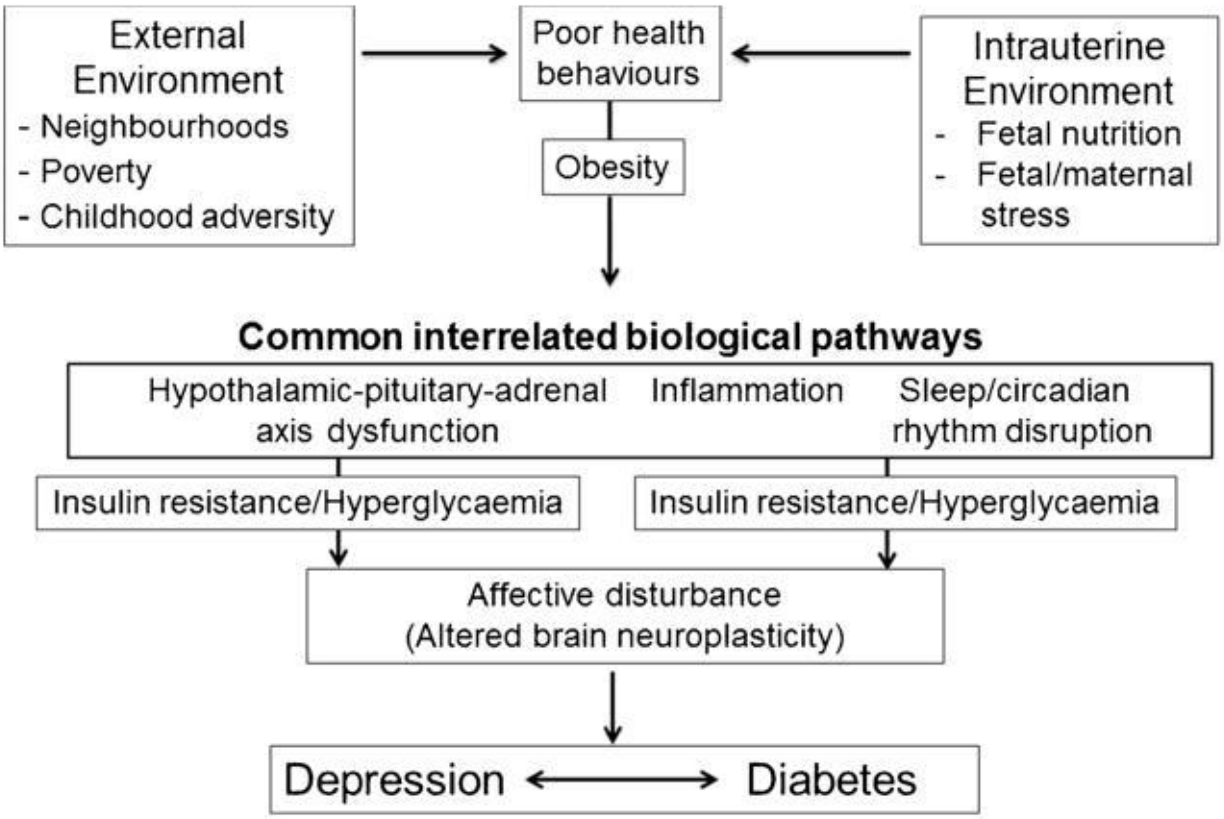

Figure 1: Shared biological mechanisms that may underlie both diabetes and depression

Inflammation. A growing body of evidence indicates that inflammation is a key shared factor in the bidirectional relationship between depression and T2DM and it has been implicated in the development of both diseases. The meta-analysis by Haapakoski et al. [15] in 2015, which included 58 studies, observed a significant elevation of the levels of inflammatory biomarkers, such as the C-reactive protein (CRP) and interleukin (IL)-6, in patients with MDD. Moreover, the relationship between inflammation and the risk of future depression was studied by Khandaker et al. [16] in 2014, where they found that elevated levels of IL-6, but not CRP, in childhood (at 9 years of age) increased the risk of future depression (at 18 years of age). In contrast, the role of inflammation in diabetes was extensively validated in a meta-analysis of 19 cohort and nested case-control studies, which found that elevated levels of CRP predicted the development of T2DM (RR, 1.26; 95% CI, 1.16–1.37; P=0.000) [17]. These findings strongly indicate that general immune activation may not be linked to depressive symptoms, but rather to specific inflammatory profiles. However, the lack of a nondiabetic control group may have critically limited the practical implications of these findings [18].

Hypothalamic-Pituitary-Adrenal Axis: Ample evidence exists to support the involvement of the HPA axis in the pathogenesis of both depression and diabetes. One meta-analysis found that depression was associated with dysregulation of the HPA axis, resulting in higher cortisol and adrenocorticotropic hormone levels, and lower corticotropin-releasing hormone levels [19]. Other studies have supported the role of HPA axis dysregulation in diabetes, as diabetes patients were found to have higher levels of cortisol [20]. Despite such evidence, there have been no sound clinical studies exacting the role of HPA axis dysregulation in the comorbidity of diabetes and

depression. However, other studies have investigated whether HPA axis hyperactivation in depression and/or diabetes may be due to variants in the HPA axis-related genes. For instance, the systematic review by Gragnoli [21] in 2014 identified the MC4R, NR3C1, and NR3C2 genes as risk genes in both T2DM and depression.

Leptin: Other researchers have suggested a role for leptin in the association between depression and diabetes. Leptin is a protein that is mainly produced by adipocytes and is responsible for the regulation of appetite, energy, and body fat and water composition [22]. Jow et al. [23] in 2006 found that leptin levels were significantly lower in patients with MDD than in healthy controls ($P<0.05$), and were negatively correlated with the severity of depression ($r=-0.067$, $P<0.05$). Similarly, the role of leptin in diabetes was supported by a meta-analysis of 11 prospective studies by Chen et al. [24] in 2014.

Genetic Factors: Several studies have attempted to explain the relationship between depression and diabetes through the presence of a common genetic variant that predisposes individuals to both conditions. For example, 20 single-nucleotide polymorphisms (SNPs) previously reported to be linked with the risk of T2DM were tested for their association, independently or in combination, with T2DM or MDD in a cross-sectional cohort of 17,404 individuals [25]. The study found that although 12 out of the 20 SNPs and the combined genotyping score were associated with T2DM (adjusted $P<0.048$), none of the SNPs were associated with MDD as evaluated by the DSM 4 diagnostic criteria (adjusted $P\geq0.09$). Furthermore, the study found no association between T2DM and depression at the phenotypic level (adjusted $P\leq0.65$). Therefore, it is difficult to establish a genetic basis for the relationship between T2DM and MDD.

Antidepressant medication (ADM) and T2DM

Antidepressants are believed to play a vital role in glucose dysregulation. Although the exact pharmacopathological pathway is yet undetermined, the side effects of ADM seem like a plausible explanation behind this association. Many ADM produce side effects like sedation which results in physical inactivity, increased appetite, weight gain which are well known risk factors for T2DM [26]. Another theory suggests that changes in serotonin levels, a hormone targeted by ADM, impacts insulin secretion resulting in dysregulation of blood glucose levels [27]. Figure 2 shows the effect of antidepressant on glucose metabolism and insulin sensitivity as proposed by Roger et.al [30].

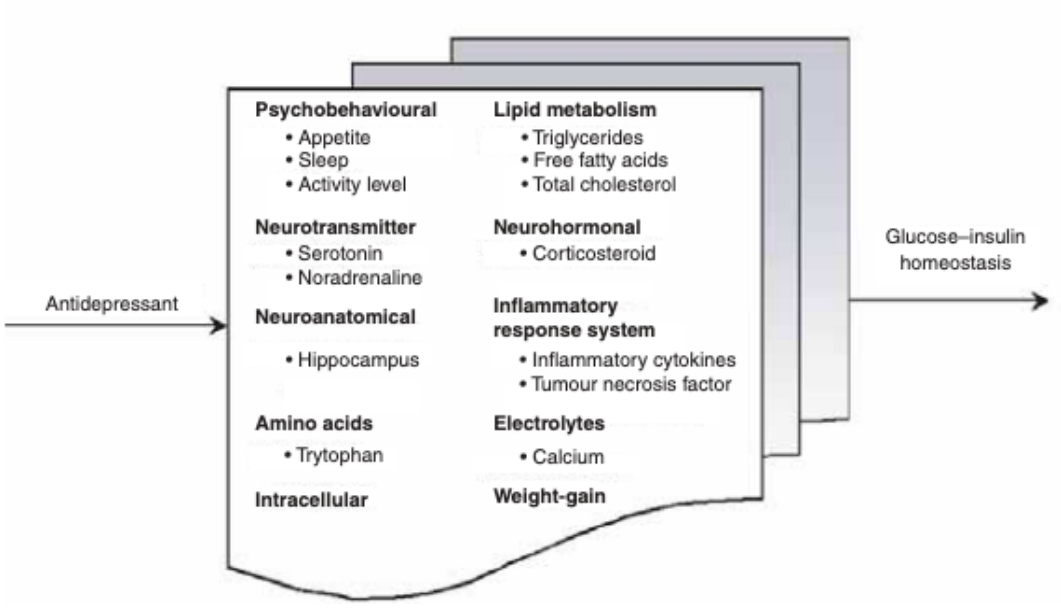

Figure 2: Antidepressant effect on glucose homeostasis.

The 2013 issue of *Diabetes Care* reported the findings of a systematic review conducted by researchers from the University of Southampton on the association of antidepressants and the risk

of T2DM [28]. The review reported that overall, people on antidepressants were more likely to have type 2 diabetes. Within that, however, the picture was somewhat confused, with some antidepressants linked to worsening glucose control, particularly with higher doses and longer duration, others linked with improved control, and yet more with mixed results. For instance, some of the studies included in the review reported that risk for type 2 diabetes almost doubled in patients using nonselective hydrazine monoamine oxidase inhibitors (e.g., phenelzine) or two types of drugs at the same time: tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) while some studies reported that serotonergic antidepressants (e.g., fluoxetine) reduced hyperglycemia, normalized glucose homeostasis and increase insulin sensitivity. Although the exact mechanism behind this association is not yet known the researchers proposed that different types of antidepressants may be linked to different amounts of risk and called for additional studies to examine the class effects of antidepressants.

Existing evidence for the association of antidepressant medication and glucose metabolism is weak as there very few studies assessing this association. Of the studies that do, the results reported are conflicting. Many of these studies have not provided sufficient detail regarding ADM dose, lifestyle of study participants and information on other confounding factors. Since, many of these studies are cross-sectional in design, it is hard to establish causality. Additionally, past studies have not considered the heterogeneity of associations across medication classes. This gap in existing literature on the association between antidepressant medication classes and the risk of developing type 2 diabetes prompted the need to conduct this systematic literature review on this topic. The present review offers an opportunity to assess impact of depression medication class on diabetes risk and better understand the benefits and risks of depression treatment, particularly as related to the widespread disease of diabetes.

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Chapter II: Manuscript-style thesis

Abstract

Introduction: Antidepressant use has increased over recent years [1,2,3]. Some studies suggest that antidepressants may affect glucose metabolism and that the associations of antidepressants to glucose metabolism may be modified by class of drug [5,7]. Our aim was to systematically assess specific classes of antidepressant medication for potential variation in longitudinal risk of type 2 diabetes.

Methods: A systematic literature search for longitudinal studies examining antidepressant classes was conducted on PubMed. Our search was restricted to papers published from 1990 to 2018 and only included studies assessing the incidence of new-onset diabetes or changes in blood glucose, HbA1c or insulin levels in adult subjects with unipolar depression treated with antidepressants. Our search was restricted to English language studies having a sample size ≥ 30.

Results: Eight studies published between 2007 and 2016 met our inclusion criteria. Research designs included 4 cohort studies, 3 case-control studies and 1 case series. A significant increase in risk of developing type 2 diabetes was reported across medication classes (Selective Serotonin Reuptake Inhibitor: 3/7, Tricyclic antidepressant: 3/6, concurrent use of Selective Serotonin Reuptake Inhibitor and Tricyclic antidepressant: 1/1, Serotonin and Norepinephrine Reuptake Inhibitor: 1/1 and Tetracyclic antidepressant: 1/1).

Conclusion: Longitudinal evidence from the past 25 years suggests that antidepressant class may impact glucose dysregulation and the risk of developing type 2 diabetes differentially. Given the possible heterogeneity of different antidepressants on the association with blood glucose levels, we suggest future studies classify the risk of type 2 diabetes according to antidepressant class,

dosage, and duration of use. Future studies that formally evaluate the risks and benefits of prescribing specific antidepressants should include potential impacts of diabetes risk.

Introduction

Use of antidepressant medications (ADM) has strongly increased over the last 20 years especially in developed countries [1,2]. For instance, the number of antidepressant users in USA has increased by 64% between 1997 to 2014[3]. This issue is becoming of utmost importance in developing countries as well, where depression is one of the leading causes of disability [3]. Antidepressants are grouped into classes based on how they affect the chemistry of brain. Although antidepressants in general work towards alleviating symptoms of depressive disorders, each class of antidepressants have different molecular structures, different mechanisms of action and different side effects [4]. In recent years, mounting evidence has linked ADM use with type 2 diabetes mellitus (T2DM) [5,6,7]. The exact mechanism behind this association is not yet determined but several possible explanations have been called upon. The side effects of ADM like weight gain, increased appetite and decrease in physical activity due to ADM's sedative effects are the most commonly proposed explanations behind this association [6]. However, very few studies have examined the impact of ADM on glycemic control and fewer still have examined the incidence of new-onset diabetes among ADM users. Many of these existing studies are cross-sectional in design, have produced conflicting results and have not considered the heterogeneity of different classes of ADM. Given the high prevalence of ADM use and diabetes in the general population, clarifying this matter is of extreme relevance for public health. The aim of this study is to systematically assess specific classes of antidepressant medication for potential variation in longitudinal risk of type 2 diabetes.

Methods

Data Sources: A systematic literature search was conducted in PubMed to identify eligible studies published between 1990 and 2018 reporting associations between ADM use and diabetes onset or changes in blood glucose, HbA1c or insulin levels. The search string showing the search strategy is reported in S1 Appendix. In addition, we hand searched the references of all articles included in the systematic review to identify additional studies of interest. Protocol registration and ethics review were not required for conducting this study.

Study Selection: The following inclusion criteria were used to select papers for this systematic review.

1. Population: Adults ≥ 18 years of age with unipolar depression (non-psychotic depression). Studies not reporting the age of study population were excluded.
2. Exposure: Antidepressant therapy with the class of antidepressant specified. Studies reporting type 2 diabetes as exposure were excluded. Study population afflicted with illnesses (other than depression) at baseline were excluded.
3. Diabetes Outcomes: This systematic review was searching for measures of association for type 2 diabetes or differences in population means of glycemic measures (like blood glucose level, HbA1C levels or insulin levels). Studies reporting gestational diabetes and/or type 1 diabetes as an outcome were excluded.
4. Study Design: Only longitudinal studies were included in this review - Case-control studies, cohort studies, randomized controlled trials, case series. All cross-sectional studies, case-reports, review studies and editorials were excluded.
5. Sample Size: ≥ 30 participants

6. Language: English
7. Published January 1, 1990 to December 31, 2018
8. Type of Publication: Full-text Original research

Study Measures: The different classes of antidepressants specified as exposure were Selective Serotonin Reuptake Inhibitor (SSRI), Tricyclic Antidepressant (TCA), Tetracyclic Antidepressant, Serotonin Norepinephrine Reuptake Inhibitor (SNRI) and concurrent use of Tricyclic Antidepressant and Selective Serotonin Reuptake Inhibitor (TCA+SSRI). The outcome measures were reported change in fasting plasma glucose levels (FGP) and/or HbA1c levels and/or insulin levels and/or diagnosis of T2DM.

Data Extraction: The selection of articles for inclusion was conducted through two screening phases. The first phase included a review of abstracts for inclusion and exclusion criteria followed by second screening phase where inclusion and exclusion criteria were applied to full-text articles. Our search yielded 331 citations from PubMed and six citations from hand searching of references. After the first screening phase of titles and abstracts, 312 citations were excluded, leaving 25 articles for full-text review. The second screening phase of full-text analysis resulted in exclusion of 17 additional papers thereby leaving eight studies for data extraction (Figure 1). The following data were extracted from the included studies: name of first author, year of publication, country, study design, duration of follow-up, sample size, mean age of the study population and class of ADM prescribed. Appendix 2 summarizes the diagnostic and inclusion-exclusion criteria employed by each study selected for this systematic review.

Results

Table 1 shows the characteristics of selected studies. Of the eight selected studies, three were case-control studies, four were cohort studies and 1 was a case-series. The selected studies were published between 2007 and 2016 and their study period ranged from 30 days to 16 years. The study sample size ranged from 40 to 766,515 participants, and the mean age of population ranged from 21 to 60 years. Four studies were from North America, 1 from Europe and 1 from Asia. The ethnicity of the study population was not specified in the selected studies . Selected studies procured data on exposure and outcome from study population's pharmacy records and/or prescription registries and/or medical records and/or self-reported questionnaires.

SSRI

Seven studies examined the association between SSRI class of antidepressant and the risk of type 2 diabetes. Three of these studies reported a significantly increased risk of diabetes among SSRI users (Table 2).

Cohort (n=4)

The Health Professional Study (1990-2006) assessed the risk of diabetes associated with antidepressant use. 4988 regular SSRI users were compared with 172521 non-users [11]. A diagnosis of diabetes was confirmed if the participants reported one or more classic symptom plus fasting plasma glucose concentration of ≥ 140 mg/dL or random plasma glucose of ≥ 200 mg/dL, at least two elevated plasma glucose values on different occasions, or treatment with hypoglycemic medication. After multivariate adjustment, SSRI use was not associated with an increased risk of T2DM (Hazards Ratio 1.17 [95%CI =0.79-1.60]).

Pan 2012 describes an analysis of the Nurses' Health Study (1996-2008) which included female nurses, among whom 25728 had a prescription of SSRI and 303466 had no history of ADM use [11]. A diagnosis of diabetes was confirmed if the participants reported one or more classic symptom plus fasting plasma glucose concentration of ≥ 140 mg/dL or random plasma glucose of ≥ 200 mg/dL, at least two elevated plasma glucose values on different occasions, or treatment with hypoglycemic medication. After multivariate adjustment, SSRI use was not associated with an increased risk of T2DM (Hazards Ratio 1.11 [95%CI =0.96-1.28]).

The Nurse's Health Study II (1993-2005) included 59796 female nurses with a prescription of SSRI and 672931 female nurses with no history of ADM use [11]. A diagnosis of diabetes was confirmed as described in Pan 2012 above. After multivariate adjustment, SSRI use was associated with an increased risk of T2DM (Hazards Ratio 1.44 [95% CI=1.27-1.44]).

In another cohort study, participants from the Netherlands Study of Depression and Anxiety were followed for 6 years to assess the bidirectional relationship between metabolic syndrome with ADM use [12]. The study included 221 frequent SSRI users (≥ 50% of time) and 1521 healthy adults with no lifetime history of depression, anxiety and ADM use. The participant's glucose levels were determined from fasting blood samples and a case of hyperglycemia was defined as fasting plasma glucose ≥ 6.1 mmol/L or use of anti-diabetes medication. ADM use in general was associated with increased metabolic syndrome abnormalities but SSRI use did not result in significant change in fasting plasma glucose levels (B=0.0001; SE=0.0023; p=0.961).

Case-control (n=3)

Among three case-control studies, two demonstrated an approximate doubling of type 2 diabetes risk in people using SSRI class of ADM.

514 patients with depression from the U.K General Practice Research Database who had received at least one new prescription for SSRI between 1990 and 2005 were randomly matched by age, sex and year of cohort entry with 1932 healthy controls [8]. Diabetes was diagnosed in people who has received at least one prescription for a diabetes drug, the recording of a diagnosis of diabetes on two separate occasions, or recording of a diagnosis of diabetes and diabetes specific test on two separate occasions. The mean follow-up time was 2.8 years for case and comparison subjects. After multivariate adjustment, recent long-term use of moderate to high daily doses of SSRI was associated with an increased risk of type 2 diabetes (Rate Ratio 2.06 [95% CI= 1.20-3.52]). In the analysis of individual antidepressant from the SSRI category, increased risk estimates were observed only for recent use of fluvoxamine (Rate Ratio 9.05 [95% CI = 1.13-2.72]) and paroxetine (Rate Ratio 1.75 [95% CI= 1.13-2.72]) administered at ≤ 20 mg daily.

A Canadian case-control study had 925 cases of depression with at least 60 days of SSRI use compared with 1,001 cases of depression with at least 60 days of TCA use [9]. Diabetes was diagnosed by physician report or the prescription of an antidiabetes medication. After multivariate adjustment, there was no difference in the risk of diabetes between SSRI users and TCA users (Odds Ratio 1.05 [95% CI 0.86-1.28]).

A Finnish occupational study compared 610 cases of depression on with at least 4 years of SSRI use prior to their T2DM diagnosis with 9350 controls selected randomly and matched by age, sex, socioeconomic position, type of employment contract, type of employer and geographic area [10]. Diabetes was defined by a physician -recorded elevated glucose in association with diabetes symptoms or two or more elevated glucose measurements. After multivariate adjustment, SSRI use of ≥ 200 defined daily dose was associated with a doubling of diabetes risk(Odds Ratio 2.02

[95% CI=1.14-2.20]) and an increased risk for SSRI use between 1-199 defined daily use (Odds Ratio 1.46 [95% CI=1.05-2.01]).

TCA

Six studies examined the association between Tricyclic antidepressants and the risk of type 2 diabetes. Three of these studies reported a significantly increased risk of diabetes among TCA users (Table 3).

Cohort studies (n=4)

The Health Professional Study (1990-2006) assessed the risk of diabetes associated with antidepressant use. 2614 regular TCA users were compared with 172521 non-users [11]. A diagnosis of diabetes was confirmed if the participants reported one or more classic symptom plus fasting plasma glucose concentration of ≥ 140 mg/dL or random plasma glucose of ≥ 200 mg/dL, at least two elevated plasma glucose values on different occasions, or treatment with hypoglycemic medication. After multivariate adjustment, TCA use was not associated with an increased risk of T2DM (Hazards Ratio 1.37 [95% CI=0.88-2.14]).

The Nurses' Health Study (1996-2008) included 12619 female nurses with a prescription of TCA and 303466 female nurses with no history of ADM use [11]. A diagnosis of diabetes was confirmed if the participants reported one or more classic symptom plus fasting plasma glucose concentration of ≥ 140 mg/dL or random plasma glucose of ≥ 200 mg/dL, at least two elevated plasma glucose values on different occasions, or treatment with hypoglycemic medication. After multivariate adjustment, TCA use was not associated with an increased risk of T2DM (Hazards Ratio1.19 [95% CI= 0.98-1.44]).

The Nurse's Health Study II (1993-2005) included 33788 female nurses with a prescription of TCA and 672931 female nurses with no history of ADM use [11]. A diagnosis of diabetes was confirmed if the participants reported one or more classic symptom plus fasting plasma glucose concentration of ≥ 140 mg/dL or random plasma glucose of ≥ 200 mg/dL, at least two elevated plasma glucose values on different occasions, or treatment with hypoglycemic medication. After multivariate adjustment, TCA use was associated with an increased risk of T2DM (Hazards Ratio 1.35 [95% CI=1.12-1.61]).

In another cohort study, participants from the Netherlands Study of Depression and Anxiety were followed for 6 years to assess the bidirectional relationship between metabolic syndrome with ADM use [12]. The study included 60 frequent TCA users (≥ 50% of time) and 1521 healthy adults with no lifetime history of depression, anxiety and ADM use. The participant's glucose levels were determined from fasting blood samples and a case of hyperglycemia was defined as fasting plasma glucose ≥ 6.1 mmol/L or use of anti-diabetes medication. ADM use in general was associated with increased metabolic syndrome abnormalities but TCA use did not result in significant change in fasting plasma glucose levels (B=0.0082; SE=0.0065; p=0.210).

Case-control (n=2)

72 patients with depression from the U.K General Practice Research Database who had received at least one prescription for TCA, Amitriptyline ≤ 38 mg daily, between 1990 and 2005 were randomly matched by age, sex and year of cohort entry with 235 healthy controls [8]. Diabetes was diagnosed in people who has received at least one prescription for a diabetes drug, the recording of a diagnosis of diabetes on two separate occasions, or recording of a diagnosis of

diabetes and diabetes specific test on two separate occasions. The mean follow-up time was 2.8 years for case and comparison subjects. After multivariate adjustment, TCA use was associated with an increased risk of type 2 diabetes (Rate Ratio 1.43 [95% CI= 1.03-1.98]).

A Finnish occupational study compared 210 cases of depression with at least 4 years of TCA use prior to their T2DM diagnosis with 9350 controls selected randomly and matched by age, sex, socioeconomic position, type of employment contract, type of employer and geographic area [10]. Diabetes was defined by a physician -recorded elevated glucose in association with diabetes symptoms or two or more elevated glucose measurements. After multivariate adjustment, TCA use of ≥ 200 defined daily dose was associated with an increased risk of T2DM (Odds Ratio 3.09 [95% CI=1.81-5.28]) while TCA use of 1-199 defined daily use was not associated with a significantly increased risk of T2DM (Odds Ratio 1.14 [95% CI=0.76-1.72]).

CONCURRENT USE OF TCA & SSRI

Only one Canadian case-control study assessed the odds of T2DM among concurrent users of TCA and SSRI [9] (table 4). The had 184 cases of depression with at least 60 days of concurrent use of TCA and SSRI compared with 1,001 cases of depression with at least 60 days of TCA use. Diabetes was diagnosed by physician report or the prescription of an antidiabetes medication. After multivariate adjustment, there was an increased risk of T2DM among concurrent users of SSRI and TCA as compared to individuals using TCA only (Odds Ratio 1.89 [95% CI =1.35 - 2.65]).

TETRACYCLIC ANTIDEPRESSANT

Only one Turkish case-series assessed the changes in glucose and insulin levels among tetracyclic antidepressant users [13] (table 5). The study included 40 underweight adult males with depression who were exposed to a tetracyclic antidepressant drug called Maprotiline 150 mg daily for 30 days. The study reported mean fasting plasma glucose levels and insulin levels measured at baseline and after 30 days. While there was no significant difference in fasting blood glucose level of participants ($p=0.527$), there was significant increase in insulin levels. The study reported an increase of 12.58 µU/mL of mean insulin level where $p<0.001$).

SNRI

A U.K based case control study assessed the risk of T2DM among 26 cases of depression with a prescription for Venlafaxine ≤ 75 mg daily, a Serotonin and Norepinephrine Reuptake Inhibitor class of ADM, TCA, between 1990 and 2005 who were randomly matched by age, sex and year of cohort entry with 62 healthy controls [8] (table 6). Diabetes was diagnosed in people who has received at least one prescription for a diabetes drug, the recording of a diagnosis of diabetes on two separate occasions, or recording of a diagnosis of diabetes and diabetes specific test on two separate occasions. The mean follow-up time was 2.8 years for case and comparison subjects. After multivariate adjustment, SNRI use was associated with an increased risk of type 2 diabetes (Rate Ratio 2.03 [95% CI= 1.18-3.48]).

To summarize the findings of this systematic review, 3 out of 7 studies on SSRI class of antidepressants, 3 out of 6 studies on TCA class of antidepressant, 1 study on concurrent use of

SSRI and TCA, 1 study on Tetracyclic class of antidepressant and 1 study on SNRI class of antidepressant reported a significant increase in risk of developing type 2 diabetes (Table 7).

Discussion

This systematic review found evidence that the risk of T2DM may vary by different classes of antidepressants. One quarter (1/4) of cohort studies and about two-thirds (2/3) of case-control studies on use of SSRI reported a significantly increased risk of T2DM. One quarter (1/4) of cohort studies and two-thirds (2/3) of case-control studies on use of TCA reported a significantly increased risk of T2DM. The individual case-control studies on concurrent use of TCA and SSRI, SNRI, and Tetracyclic ADM each showed a significantly increased risk of developing T2DM. However, these findings are limited to the small number of studies examining ADM class. Among all the classes of antidepressants included in this review, the risk of developing T2DM was highest for high doses of TCA use followed by SNRI, concurrent use of SSRI and TCA and higher doses of SSRI only (OR=3.09 [95% CI=1.81-5.28] , RR=2.03 [95% CI=1.18-3.48], OR=2.02 [95% CI=1.14-2.20, OR=1.89 [95% CI=1.35-2.65] respectively). Taken together, these findings suggest that each class of antidepressant presented a moderately elevated risk of type 2 diabetes after covariate adjustment and the risk varies for different classes of ADM.

The 2013 issue of Diabetes Care reported the findings of a systematic review conducted by researchers from the University of Southampton on the association of antidepressants and the risk of T2DM [43]. The review reported that overall, people on antidepressants were more likely to have type 2 diabetes. Within that, however, the picture was somewhat confused, with some antidepressants linked to worsening glucose control, particularly with higher doses and longer

duration, others linked with improved control, and yet more with mixed results. For instance, some of the studies included in the review reported that risk for type 2 diabetes almost doubled in patients using nonselective hydrazine monoamine oxidase inhibitors (e.g., phenelzine) or two types of drugs at the same time: tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) while some studies reported that serotonergic antidepressants (e.g., fluoxetine) reduced hyperglycemia, normalized glucose homeostasis and increase insulin sensitivity. Although the exact mechanism behind this association is not yet known the researchers proposed that different types of antidepressants may be linked to different amounts of risk and called for additional studies to examine the class effects of antidepressants, a research gap we attempted to fill without systematic review.

Previous literature reporting on possible mechanisms of ADM impact on human biology support the premise that ADM class may influence diabetes risk. In past years, most research on the metabolic effects of psychotropic drugs was focused on antipsychotics, especially second-generation antipsychotics, with their well-acknowledged ability to induce metabolic syndrome and diabetes [22-24]. The supposed mechanism by which some ADM may worsen glucose metabolism could involve weigh gain, which could occur even in the short-term. In a meta-analysis conducted on 116 studies, the authors found out that some, although not all, ADM could significantly increase weight even within the first 12 weeks of treatment, further increasing body weight over the long-term [30]. Since weight gain is probably the most relevant determinant of diabetes through the induction of insulin-resistance, the observed association between ADM use and diabetes is not surprising. Five out of eight studies selected for this review reported about weight gain among ADM users. However, we observed that different ADM classes had different associations with weight gain, which is another reason to support findings for potential heterogeneity by drug class.

The HPFS study, NHS – I and NHS – II noted that weight gain was a common side effect in short term and long term treatment with TCA but there was evidence of stable weight or even weight loss with the use of SSRI [11]. Similarly, Andersohn et al. reported higher weight gain among TCA users while weigh changes associated with SSRI were complex where there was an initial stable weight or even weight loss among SSRI users followed by weight gain if used for longer periods [8]. Contradicting this was Kivimaki's findings on increase in weight among SSRI users as compared to non-users [10]. Hiles also reported a significant increase in weight circumference among ADM users in general but more so among TCA users [12]. The results of case series by Pinar indicate that Tetracyclic ADM induced weight gain in patients with depressive disorder which seems to be related to increase in blood ghrelin levels as well as increased insulin resistance [13].

On the contrary, other studies considered ADM as neutral or even beneficial on glucose homeostasis, having previous studies demonstrated that ADM use leads to improvements in glucose and insulin levels over the short-term [25,26]. In a recent study, better insulin sensitivity was only associated with SSRIs whereas use of tricyclics was associated with higher HOMA-IR scores [27], likely supporting previous hypotheses by which ADM with adrenergic and cholinergic activity may determine an increase in glucose [28,29]. However, the improvement in insulin sensitivity from ADM may be due to resolution of depressive symptoms and not merely to ADM exposure, since only responders and remitters to ADs showed it [26]. Therefore, future research will be needed to examine different pharmacologic agents and mechanisms impacting insulin sensitivity, beta cell function, and diabetes risk and pathogenesis.

ADM heterogeneity on diabetes risk and potential mechanisms may be further elucidated by medication side effects. Common side effects associated with ADM use include SSRI-induced nausea or dry mouth and constipation with TCA use. On the other hand, a pharmacodynamic-based classification, built on the capacity of single ADM to interact with those receptors linked with weight gain and metabolic abnormalities, could be more useful. A previous clinical study showed that only exposure to ADM with high H1-receptor (H1-R) affinity, and not exposure to ADs as a whole, was associated with metabolic syndrome in patients with bipolar disorder [41]. It is plausible to expect that the weight-gain associated with the use of high H1-R affinity ADs can eventually translate in a higher risk of developing diabetes. This hypothesis is partially supported by the study of Derjiks and colleagues that used the World Health Organization (WHO) Adverse Drug Reaction Database to evaluate the effect of ADs on glucose metabolism. The authors found that hyperglycemia was associated with the use of ADs with high affinity for H1 and 5HT2c receptors [42]. In order to provide more accurate and informative results, future studies should be powered to evaluate diabetes risk of single ADM or more information should be included on dose and duration of class of ADM prescribed.

There are several limitations that may impact our study findings. First, diabetes itself can trigger the risk for depression and lead, by reverse causation, to the prescription of ADs. In this review, we managed this possibility by excluding cross-sectional studies, and we only included studies that contained longitudinal data. Second, patients who get ADM may have other behaviors that impact diabetes risk which may confound the findings of this study. For example, ADM are typically prescribed to patients who often engage in unhealthy lifestyles such as unbalanced diet, either poor or, in case of atypical depression, characterized by overeating of high glycemic index carbohydrates. Asthenia (lack of energy) and lack of motivation also leads to marked decrease of

physical activity in these patients. Furthermore, they may fail to attend medical examinations and checkups, thereby increasing the likelihood of undetected diabetes. Third, studies may not have accurately categorized depression cases. Residual symptoms such as fatigue and lack of energy might not qualify for a depressive episode, thus being overlooked in these patients while still increasing the risk of glucose abnormalities and diabetes. Fourth, apart from medication exposures, depression itself is a well-acknowledged risk factor for diabetes [38,39,40], and patients are treated with ADM most often due to underlying depression. Fifth, the search for potential papers was limited to one search engine only (PubMed). This review did not cover all classes of ADM, potentially due to publication bias. Other classes of antidepressants namely, monoamine oxidase inhibitor (MAO), atypical antidepressants and a combination of antidepressants were not covered by the studies included in this review.

A major strength of this review is that all studies were longitudinal in design, reducing the possibility of reverse causation in interpretation of results. Additionally, the study search for this review spanned across 28 years (1990 to 2018), thereby providing most updated results on this research area from another review published in 2013. The study population for this review is somewhat diverse in nature. There are three studies from USA, one from Canada, one from Finland, one from U.K and one from Turkey, potentially improving the generalizability of the findings of this review. Nevertheless, future studies that are more inclusive of diverse settings (e.g., development, income level, education level, ethnicity) should be considered.

In conclusion, this systematic literature review has attempted to synthesize the risk of developing type 2 diabetes by different classes of antidepressants and found that the risk varies for different classes. Given the possible heterogeneity of different antidepressants on the association with blood glucose levels, we suggest future studies classify the risk of type 2 diabetes according to

antidepressant class, dosage, and duration of use. We also recommend future clinical trials of individual antidepressants report adverse metabolic consequences, especially hyperglycemia. Future studies that formally evaluate the risks and benefits of prescribing specific antidepressants should include potential impacts of diabetes risk.

Tables and Figures

Figure 1: Flow diagram of the systematic review

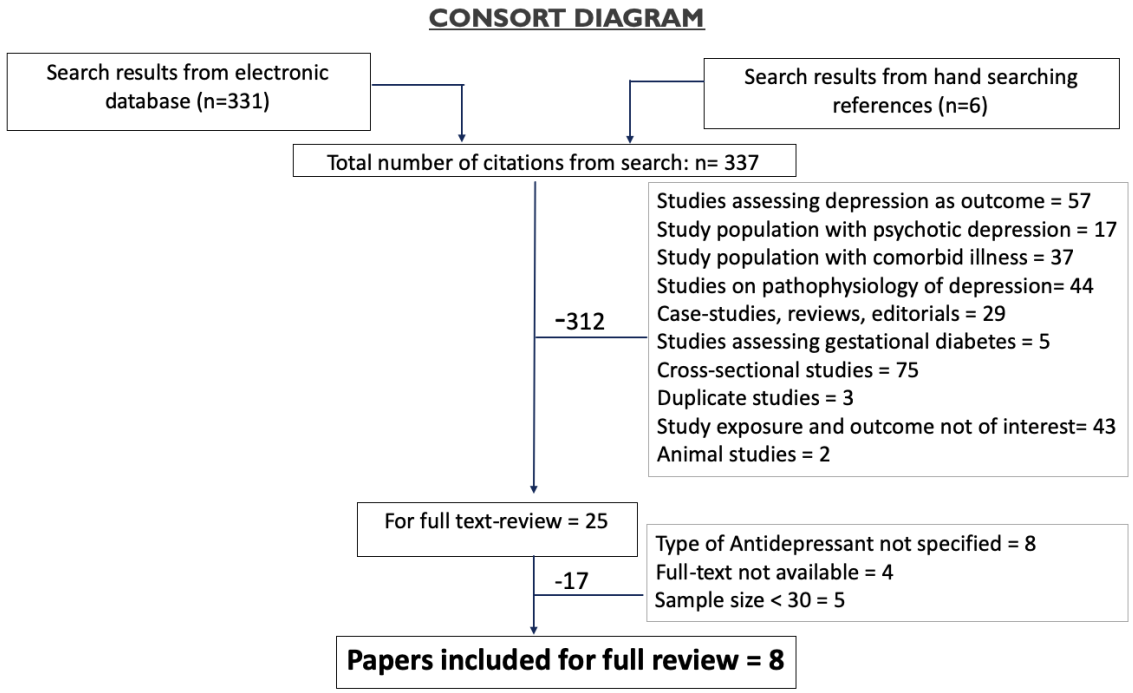

Table 1: Characteristics of studies included in the systematic review

Author & Year	Country	Study Design	Duration of follow-up	Sample Size	Mean Age in years (SD)	Class of ADM prescribed
Andersohn 2009	U.K	Case-Control	15 years	976	56 (13)	TCA, SSNRI, SSRI
Brown 2007	Canada	Case-control	4.1 years	2,110	53.6 (16.4)	SSRI, TCA, SSRI+TCA
Hiles 2016	Netherlands	Cohort	6 years	1,802	48.20 (13.2)	TCA, SSRI
Kivimaki 2010	Finland	Case-control	4.8 years	10,170	56.5	SSRI, TCA
Pan 2012	USA	Cohort	16 years	180,123	56.35	SSRI, TCA
Pan 2012	USA	Cohort	12 years	341,813	60.6	SSRI, TCA
Pan 2012	USA	Cohort	14 years	766,515	38.6	SSRI, TCA
Pinar 2008	Turkey	Case-series	30 days	40	21.0 (1)	Tetracyclic AD

Legend Table 1: Abbreviations included are SSRI (Selective Serotonin Reuptake Inhibitor), TCA (Tricyclic Antidepressant), SSNRI (Serotonin Norepinephrine Reuptake Inhibitor), AD (Antidepressant)

Table 2: Results for SSRI

Author & Year	Study type	Exposure Group/ Case Group	Unexposed Group/ Control Group	Measure of Association	Adjustment Variables
Hiles 2016	Cohort	Adults with frequent use (≥ 50% of time) of SSRI Dose: not reported 221 subjects with hyperglycemia.	No AD use	Associations of SSRI use with fasting plasma glucose levels using Generalized Estimating Equations B=0.0001; SE=0.0023; p=0.961	Age, sex, education, smoking status, alcohol use and physical activity.
Pan 2012 (HPFS)	Cohort	Regular use of SSRI during the preceding 2 years. Dose: Not specified. 33 subjects with incident T2DM	No AD use	Hazards Ratio (95% CI) = 1.17 (0.79, 1.60)	Age, ethnicity, marital status, living status, smoking, alcohol intake, multivitamin and aspirin use, physical activity, family history of diabetes, major comorbidities, dietary score, BMI.
Pan 2012 (NHS I)	Cohort	Prescription of SSRI. Dose: not reported. 206 subjects with incident T2DM	No AD use	Hazards Ratio (95% CI) = 1.11 (0.96, 1.28)	Age, ethnicity, marital status, living status, smoking, alcohol intake, multivitamin and aspirin use, physical activity, family history of diabetes, major comorbidities, dietary score, BMI, MHI -5 score.
Pan 2012 (NHS II)	Cohort	Prescription of SSRI. Dose: not reported. 306 subjects with incident T2DM.	No AD use	Hazards Ratio (95% CI) = 1.44 (1.27, 1.64)	Age, ethnicity, marital status, living status, smoking, alcohol intake, multivitamin and aspirin use, physical activity, family history of diabetes, major comorbidities, dietary score, BMI, MHI -5 score.
Andersohn 2009	Case-control	Participants with at least one prescription of SSRI Dose: not reported. 514 cases	1,931 controls selected randomly, matched by age (± 2 years), sex and year of cohort entry.	Rate Ratio (95% CI) of developing T2DM = 2.06 (1.20,3.52)	BMI, smoking, hypertension, hyperlipidemia, recent use of beta-blockers, thiazides, antipsychotics, carbamazepine, phenytoin, valproate, lithium, glucocorticoids

Brown 2007	Case-control	Participants with at least 60 days of SSRI use Dose: not reported. 925 cases	1,001 controls with at least 60 days of TCA use.	Odds Ratio (95% CI) = 1.05 (0.86, 1.28)	Sex, age, number of physician visits, use of augmentation therapy – carbamazepine, lithium, valporic acid, thyroid replacement, other.
Kivimaki 2010	Cohort	SSRI use over a fixed period of 4 years prior to diagnosis of T2DM Dose: 1-199 and ≥ 200 defined daily doses. 610 cases	9,350 controls selected randomly, matched for age-group, sex, socioeconomic position, type of employment contract, type of employer and geographic area.	Odds Ratio (95% CI) =1.46 (1.05, 2.01) for 1-199 defined daily dose of SSRI. Odds Ratio (95% CI) = 2.02 (1.14, 2.20) for ≥ 200 defined daily dose of SSRI.	Sex, age, prevalent physical disease (hypertension, coronary heart disease, cerebrovascular disease and cancer)

Legend Table 1: Abbreviations included are SSRI (Selective Serotonin Reuptake Inhibitor), AD (Antidepressant), T2DM (Type 2 diabetes mellitus), BMI (Body Mass Index), MIH-5 (Mental Health Inventory version 5)

Table 3: Results for TCA

Author & Year	Study Design	Exposure Group/ Case Group	Unexposed Group/ Control Group	Measure of Association	Adjustment Variables
Hiles 2016	Cohort	Adults with frequent use (≥ 50% time) of TCA Dose: not reported 60 subjects with hyperglycemia	No AD use	Associations of TCA use with Fasting Plasma glucose levels using Generalized Estimating Equations B=0.0082; SE=0.0065; p=0.210	Age, sex, education, smoking status, alcohol use and physical activity.
Pan 2012 (HPFS)	Cohort	Regular use of TCA during the preceding 2 years. Dose: Not specified. 20 subjects with incident T2DM	No AD use	Hazards Ratio (95% CI) =1.37 (0.88, 2.14)	Age, ethnicity, marital status, living status, smoking, alcohol intake, multivitamin and aspirin use, physical activity, family history of diabetes, major comorbidities, dietary score, BMI.
Pan 2012 (NHS I)	Cohort	Prescription of TCA. Dose: not reported. 109 subjects with incident T2DM	No AD use	Hazards Ratio (95% CI) =1.19 (0.98,1.44)	Age, ethnicity, marital status, living status, smoking, alcohol intake, multivitamin and aspirin use, physical activity, family history of diabetes, major comorbidities, dietary score, BMI, MHI -5 score.
Pan 2012 (NHS II)	Cohort	Prescription of TCA. Dose: not reported. 137 subjects with incident T2DM	No AD use	Hazards Ratio (95% CI) =1.35 (1.12, 1.61)	Age, ethnicity, marital status, living status, smoking, alcohol intake, multivitamin and aspirin use, physical activity, family history of diabetes, major comorbidities, dietary score, BMI, MHI -5 score.
Anderson 2009	Case-control	Participants with at least one prescription of TCA Dose: Amitriptyline ≤ 38 mg daily 72 cases	235 controls selected randomly, matched by age (± 2 years), sex and year of cohort entry.	Rate Ratio (95% CI) of developing T2DM = 1.43 (1.03, 1.98)	BMI, smoking, hypertension, hyperlipidemia, recent use of beta-blockers, thiazides, antipsychotics, carbamazepine, phenytoin, valproate, lithium, glucocorticoids
Kivimaki 2010	Case-control	TCA use over a fixed period of 4 years prior to diagnosis of T2DM Dose: 1-199 and ≥ 200 defined daily doses.	9,350 controls selected randomly, matched for age-group, sex, socioeconomic position, type of employment contract, type of employer and geographic area.	Odds Ratio (95% CI) = 1.14 (0.76, 1.72) for 1-199 defined daily dose of TCA	Sex, age, prevalent physical disease (hypertension, coronary heart disease, cerebrovascular disease and cancer)

		210 cases		Odds Ratio (95% CI) = 3.09 (1.81, 5.28) for defined daily dose of ≥ 200 TCA	

Legend Table 3: Abbreviations included are TCA (Tricyclic Antidepressant), AD (Antidepressant), T2DM (Type 2 diabetes mellitus), BMI (Body Mass Index), MIH-5 (Mental Health Inventory version 5)

Table 4: Results for concurrent use of TCA and SSRI

Author & Year	Study design	Exposure Group/ Case Group	Unexposed Group/ Control Group	Measure of Association	Adjustment Variables
Brown 2007	Case-control	Participants with at least 60 days of concurrent use of TCA and SSRI. Dose: not reported. 184 cases	1,001 controls with at least 60 days of TCA use.	Odds Ratio (95% CI) = 1.89 (1.35, 2.65)	Sex, age, number of physician visits, use of augmentation therapy – carbamazepine, lithium, valporic acid, thyroid replacement, other.

Legend Table 4: Abbreviations included are SSRI (Selective Serotonin Reuptake Inhibitor), TCA (Tricyclic Antidepressant) AD (Antidepressant), T2DM (Type 2 diabetes mellitus).

Table 5: Results for Tetracyclic Antidepressant

Author & Year	Study design	Exposure Group/ Case Group	Unexposed Group/ Control Group	Measure of Association	Adjustment Variables
Pinar (2007)	Case-series	40 underweight adult males diagnosed with depressive disorder Dose: Maprotiline 150 mg daily	Same subjects followed over 30 days.	Mean (± SD) for fasting plasma glucose and insulin level Day 0: - Glucose:89.00 mg/dL (±6.52) - Insulin:11.30 µU/mL (±1.51) Day 30: - Glucose: 87.97 mg/dL (±7.03) - Insulin: 23.88 µU/mL (±8.58) Glucose: p=0.527 Insulin: p<0.001	Not reported

Table 6: Results for SNRIs

Author & Year	Study design	Drug Group	Comparison Group	Measure of Association	Adjustment Variables
Andersohn (2009)	Case-control	Participants with at least one prescription of a SNRI Dose: Venlafaxine ≤ 75 mg daily 26 cases	62 controls selected randomly, matched by age (± 2 years), sex and year of cohort entry.	Rate Ratio (95% CI) for T2DM = 2.03 (1.18, 3.48)	BMI, smoking, hypertension, hyperlipidemia, recent use of beta-blockers, thiazides, antipsychotics, carbamazepine, phenytoin, valproate, lithium, glucocorticoids

Table 7: Summary of findings

Class of AD	No. of studies	Summary of results
SSRI	7	3 studies reported a significant association between SSRI use and risk of developing type 2 diabetes.
TCA	6	2 studies reported significant association between TCA use and risk of developing type 2 diabetes while 1 study reported increased risk of type 2 diabetes among people using higher doses of TCA.
SSRI + TCA	1	Concurrent use of SSRI and TCA was associated with a significantly increased risk of type 2 diabetes compared to use of TCA alone.
Tetracyclic Antidepressant	1	Study reported significant increase in insulin levels.
SSNRI	1	Study reported increased risk of type 2 diabetes associated with recent long-term use of Venlafaxine.

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Supporting Information

S1 Appendix. Search string used for the systematic review.

S2 Appendix. Data Extraction table.

Chapter III: Public Health Implications

Debate around the side effects of antidepressants, one of the most prescribed groups of drugs worldwide [1], continues. First there was a concern that antidepressant medication may, with rather tragic irony, increase suicide risk. Then, meta-analyses suggested that there was no significant benefit of antidepressants over placebo in treating patients with minor depression [2]. The most recent controversy relates to a series of studies, including one in the present issue of Diabetologia, suggesting that long-term use of antidepressants might predispose individuals to type 2 diabetes [3–5].

This systematic review found that a significant increase in risk of type 2 diabetes was reported across different classes of ADM (SSRI: 3/7, Tricyclic antidepressant: 3/6, concurrent use of SSRI and TCA: 1/1, SNRI: 1/1 and Tetracyclic antidepressant: 1/1) and the risk of developing T2DM was highest for high doses of TCA use followed by SNRI, concurrent use of SSRI and TCA and higher doses of SSRI only (OR=3.09 [95% CI=1.81-5.28] , RR=2.03 [95% CI=1.18-3.48], OR=2.02 [95% CI=1.14-2.20, OR=1.89 [95% CI=1.35-2.65] respectively). Taken together, these findings suggest that each class of antidepressant presents a moderately elevated risk of type 2 diabetes after covariate adjustment and the risk varies for different classes of ADM. These findings warrant and intensive examination of this topic with rigorous, longitudinal research in U.S populations as well as other populations globally. Based on the results of this review, we recommend future studies stratify the association between different classes of antidepressants and risk of type 2 diabetes and include daily dosage. We also strongly suggest assessment of glucose metabolism be included in any future randomized controlled trials of antidepressants to report adverse metabolic consequences of treatment.

What further supports the need for more rigorous research is what is known now about diabetes development and heterogeneity of pathophysiology across populations. Antidepressants are believed to play a vital role in glucose dysregulation. Although the exact pharmacopathological pathway is yet undetermined, the side effects of ADM seem like a plausible explanation behind this association. Many ADM produce side effects like sedation which results in physical inactivity, increased appetite, weight gain which are well known risk factors for T2DM [6]. Another theory suggests that changes in serotonin levels, a hormone targeted by ADM, impacts insulin secretion resulting in dysregulation of blood glucose levels [7].

Existing evidence for the association of antidepressant medication and glucose metabolism is weak as there very few studies assessing this association. Of the studies that do, the results reported are conflicting. Many of these studies have not provided sufficient detail regarding ADM dose, lifestyle of study participants and information on other confounding factors. Since, many of these studies are cross-sectional in design, it is hard to establish causality. Additionally, past studies have not considered the heterogeneity of associations across medication classes. Antidepressants are grouped into classes based on how they affect the chemistry of brain. Moreover, antidepressants in general work towards alleviating symptoms of depressive disorders, each class of antidepressants have different molecular structures, different mechanisms of action and different side effects [8].

Antidepressants are prescribed in high proportion to those who develop depression, contributed by the historical introduction of various drugs into medical practice. The introduction of tricyclic antidepressants (TCAs) in the late 1960s, followed by that of selective serotonin re-uptake inhibitors (SSRIs) in the 1980s, together with the increase of long-term prescriptions (in the 1990s and 2000s) and to the more recent use of higher doses of antidepressants, have contributed to a

tendency toward over prescribing of antidepressants [9]. With the increasing number of antidepressant users around the world and the possibility of worsening glycemic control with antidepressant use, it is important to consider potential ramifications of increased dysglycemia, including diabetes that may result from antidepressant medications.

This systematic review is an attempt to gather useful information that could help inform prevention strategies of both depression and diabetes, early diagnosis of diabetes, availability of integrated and collaborative health care systems for patients, and ensuring awareness about different lifestyle changes that could benefit high-risk patients.

The findings of our review offer an opportunity to assess impact of depression medication class on diabetes risk and better understand the benefits and risks of depression treatment, particularly as related to the widespread disease of diabetes. Given the narrow scope of this research, the findings may not be enough to bring about changes in clinical practice of prescribing antidepressants, but it can be used to help define risks when considering a drug regime for depression. Additional studies along the lines of this review can help endorses the concept of integration of mental health assessment in primary health care systems, particularly in the domain of diabetes which can aid in the early detection and improved management of this chronic debilitating condition. In addition, a more precise understanding of the underlying mechanisms of this bidirectional relationship would ideally open the door for new and advanced therapeutic and preventive options for both conditions in the near future.

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