

## The Impact of Antidepressants on Blood Sugar and Lipid Profiles in Diabetic Patients: A Comprehensive Review

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### Abstract

Diabetes prevalence and mortality are rising worldwide. Despite multiple treatments, optimal blood sugar control in type 2 diabetes remains challenging. This has prompted interest in whether antidepressants could influence glycemic management. However, studies examining their effects on blood glucose have reported inconsistent and sometimes conflicting results. This article will discuss the effects that different antidepressants may have on blood sugar and lipid levels. We plan to focus chiefly on tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors (SNRIs). To achieve the aim of the present study, we searched PubMed using separate strategies that combined Title/Abstract keywords and MeSH terms related to type 2 diabetes and different classes of antidepressants (SSRIs, SNRIs, TCAs, agomelatine, and benzodiazepines) to ensure comprehensive coverage of relevant evidence. For type 2 diabetic patients, the principal achievement was that SSRIs of all types could reduce blood sugar, and they particularly had been shown to stimulate the body's own insulin response. Patients lost weight and blood sugar control improved with fluoxetine. The purpose of this review is to describe the existing information and also point out shortcomings in previous studies, as well as providing directions for future research on how various antidepressants affect their patients' metabolic outcomes alongside potential mental status changes. These relationships are important to understand, not only for planning effective treatments for diabetes but also in order to manage the complicated metabolic-psychiatric continuum.

**Keywords:** Anti-depressive agents, Blood glucose, Dyslipidemias, Diabetes mellitus

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## Introduction

Diabetes is one of the major problems affecting the provision of health care, with increased rates in the last three decades and considerable morbidity and mortality globally (1,2). Despite the availability of many drugs for treating diabetes, many people have difficulties controlling their blood sugar levels and managing the complications that arise (3,4). Therefore, efforts to find effective medicines for optimal blood sugar control continue (4). Several studies have evaluated the effect of antidepressants on blood sugar level in patients (5). There are different types of antidepressants including Tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), selective noradrenaline reuptake inhibitors (SNRIs), monoamineoxidase inhibitors (MAOIs), 5-hydroxytryptamine (5-HT) Receptor Modulators and Tetracyclic and Unicyclic Antidepressants (6). They exert their antidepressant effect through different specific pathways. For example, SSRIs like fluoxetine induce their effect through serotonin reuptake inhibition (7). While SNRIs bind to both the serotonin and the norepinephrine transporters. TCAs work by inhibiting the reuptake of 5-HT and norepinephrine to play their antidepressant role (6).

In accordance with the study's findings, some anti-depressants increase blood glucose levels and impair insulin sensitivity. However, there are some that enhance glycemic control and improve insulin response (8). Thus, certain drugs, especially SSRIs, like fluoxetine, have shown positive effects on regulating of blood sugar and may be recommended for treating depression in patients with type 2 diabetes (9,10).

Studies have demonstrated that treating diabetic patients with associated depression using fluoxetine can reduce depressive symptoms and improve blood sugar levels. This leads to improved well-being, better adherence to diabetic medication regimens and

improvements in blood glucose and lipid indices through molecular pathways (9,11). Therefore, further research is needed to determine if these drugs could provide metabolic benefits to patients with type 2 diabetes who do not have depression. To address this gap, studies were conducted to investigate how specific medications affect metabolic indicators in diabetic patients. The aim of this review was to identify standard antidepressants (SSRIs, SNRIs and TCA) that have been studied in clinical trials and their outcomes. Additionally, the review aimed to determine if these antidepressants could have a positive impact on blood sugar and lipid profile in diabetic patients even in the absence of depression.

### Selective Serotonin Reuptake Inhibitors (SSRI)

#### *Effects of SSRI on regulating blood sugar*

This class of antidepressants is represented by the drugs fluoxetine, citalopram, escitalopram, fluvoxamine, sertraline and paroxetine (12). SSRIs are thought to exert their therapeutic effects through serotonin reuptake inhibition. They are given their name because they don't have much of an effect on the reuptake of norepinephrine or dopamine (13). Often, adequate clinical activity and saturation of the 5-HT transporters are achieved at starting dosages. The most selective inhibitors of serotonin reuptake are citalopram and escitalopram. They exert little inhibition of norepinephrine or dopamine reuptake, and have very low affinities for histamine, H<sub>1</sub>, GABA, or benzodiazepine receptors. The other SSRIs have a similar profile, except that fluoxetine is a weak inhibitor of norepinephrine reuptake and binds with 5-HT<sub>2C</sub> receptors; sertraline moderately inhibits reuptake of norepinephrine and dopamine, while paroxetine has a greater effect. It has anticholinergic activity at higher dosages and binds to nitric oxide synthase (14). According to recent investigations

among these drugs only the impact of fluoxetine has been evaluated regarding its effects on blood sugar/blood fat in non-depressed diabetic patients. Fluoxetine is an antidepressant that has been in clinical use for close to three decades in the treatment of major depressive disorder as well as other mental disorders with great success in treatment efficacy (15). As a result, this medicine is among the preferred drugs for treating diabetic patients suffering from depression at the same time (16,17). The studies conducted to monitor post fluoxetine therapy show that the drug has another role in controlling blood sugar levels (9). This appears to be partly due to improvements in depression and better adherence to the drug regimen and partly because of increased insulin secretion and facilitation of glucose uptake into targeted cells by the drug itself (11,18).

Fluoxetine has also been known to treat other non-psychiatric diseases, such as obesity. Various mechanisms for the use of fluoxetine in the treatment of obesity have been documented, making it one of the suggested therapies for obesity (19). The results of clinical studies showed that serotonergic drugs such as fluoxetine were effective in reducing appetite before and after eating fixed caloric portions, pre-meal appetite, weight loss and actual food intake. Furthermore, fluoxetine inhibits the proliferation of Adipose-derived stem cells (ASCs) by autophagy. Fluoxetine also suppresses the differentiation of ASCs into adipocytes (20). It is worth mentioning that several investigations have determined that this medication induces weight reduction and enhances blood lipid markers (9,21). Some parts of the literature suggest that fluoxetine has a neutral impact on weight in the short term and weight monitoring through further investigation is required to determine its long-term effects (22).

Six investigations have been conducted previously on how fluoxetine reduces blood sugar levels in overweight diabetic patients (23-28). It is important to note that these

patients were only receiving fluoxetine as their primary treatment for weight loss, with no additional treatment regimens. Blood sugar levels were also monitored to determine if fluoxetine helped in controlling blood sugar. These were randomized clinical trials involving the administration of either fluoxetine or a placebo with follow-ups ranging from four to twenty-four weeks. All studies assessed blood glucose indicators, while lipid profile indicators were tested in three of them. HbA1c levels were measured in all trials and showed a decrease in the fluoxetine group compared to the placebo group in four studies(23,24,26,28) but there was no significant change in the two studies (25,27).

One of these trials was carried out by Gray et al. in which 48 male and female, obese type diabetics on insulin were randomized to receive fluoxetine 60 mg once daily or a placebo for 24 weeks. Subjects were asked to monitor glucose levels at home every day and received instruction in a 1200 kcal American Diabetic Association (ADA) diet. Those receiving the active drug lost 8 kg more weight, on average, than those given placebo. After active treatment, the HbA1c levels of fluoxetine-treated subjects were significantly lower than those of the placebo group (28).

Breum et al. decided to conduct a 12-month randomized double-blind clinical trial with 40 obese patients suffering from NIDDM or IGT as subjects. Participants were randomized to receive either 60 mg fluoxetine (F) or placebo daily on a 5.0-MJ/d diet of > 50 %. Both groups showed significant weight loss without any significant differences between groups. Fasting glucose levels declined significantly in the F group during the study period ( $2.1 \pm 3.6$  mmol/L,  $P < 0.05$ ), whereas FBS remained unchanged in the P group ( $0.8 \pm 1.2$  mmol/L, NS). Glycemic control was considerably improved in the two mentioned groups with a tendency for a larger decline in HbA1c in the F group ( $P < 0.05$ ) (23).

A randomized, double-blind, parallel research study was conducted with 30-obese

patients to evaluate the safety and efficacy of fluoxetine in individuals aged over 60 with type 2 diabetes. The effects of fluoxetine at a daily dosage of 60 mg were compared to a placebo group. The individuals, all of whom were treating their diabetes with diet, had an HbA1c level of less than 14% and a BMI greater than 29 kg/m<sup>2</sup>. In compared to the placebo group, people taking fluoxetine lost weight significantly throughout the course of the research, with reductions of 2.6 kg at 3 months and 3.9 kg at 6 months. Furthermore, the fluoxetine group showed better glycemic control, with a 0.9% decline in baseline HbA1c levels at 4 and 6 months ( $P < 0.02$ ). However, no consistent improvement in fasting blood glucose levels was seen. The fluoxetine and placebo groups had comparable rates of adverse events (24).

In a double-blind parallel study conducted by Daubresse et al, 82 noninsulin-dependent diabetics who were moderately obese (BMI= 30-39 kg/m<sup>2</sup>) were given placebo (P) or fluoxetine (F), in addition to their usual antidiabetic treatment. Thirty-nine received 60 mg of fluoxetine a day and 43 received the placebo. Upon admission, both groups had comparable values of weight loss, metabolic control and serum lipids. After 3 weeks, the fasting blood glucose in group F had declined (- 1.5 vs, - 0.4 mmol/L), and after 8 weeks this trend became even clearer (-1.7 vs, -0.02 mmol/L). In group F, HbA1c decreased from 8.5 % to 7.7 %, and in group P it declined from 8.6 % to 8.3 %, but the changes were not statistically significant. Comparing to the placebo group fasting insulin levels significantly declined after 3 and 8 weeks in group F. Moreover, after 8 weeks, the mean triglyceride level was also considerably decreased in group F ( $P = 0.042$ ) (27).

Another randomized, double-blind, placebo-controlled trial measured glucose disposal following insulin response in 12 obese patients with type 2 diabetes on diet alone before and after four weeks of treatment with either placebo or fluoxetine at the dose level of 60 mg once a day. In the fluoxetine group, fasting

plasma glucose decreased from 10.0±0.9 to 8.9±1.4 mmol/l; while in the placebo group, it declined only slightly from 10.9±1.5 to 10.5±1.7. Furthermore, changes in HbA1c were from 6.7±0.6 to 7.1±0.8 among the fluoxetine group and from 7.0±0.9 to 6.8±0.5 among placebo group patients. Between the two groups, the changes from baseline to the end of the trial were not significant for neither FBS nor HbA1c (25).

A 12-month, double-blind trial was conducted in 19 obese type 2 diabetic patients to assess the effect of fluoxetine (60 mg daily) compared to placebo. At the end of three months, six months, nine months, and one year, there was a significant decrease in median body weight. After 3 months, there was a notable decrease of 1.9 mmol/l median fasting blood glucose levels and a substantial reduction of 0.7% in HbA1c levels. However, there was no significant improvement observed in either measure after 9 or 12 months of fluoxetine medication compared to a placebo. While there was no significant change in blood cholesterol levels throughout the course of the year, individuals taking fluoxetine showed a significant pattern in their serum triglyceride levels. These levels decreased to 0.5 mmol/l after 3 months of medication, but did not continue to decrease there after (26).

However, it needs to be mentioned that the discussed studies were published between 1992 and 1997 predating the year 2000. After conducting these studies over the years, a connection was found between the use of fluoxetine and the improvement of blood glucose markers.

Therefore; two studies were designed to evaluate the impact of fluoxetine on blood glucose in patients with uncontrolled diabetes without obesity. One of these studies, a before-after study conducted in 2002 (29), was followed by the RCT that was implemented in 2008 (30) comparing the effects of fluoxetine and alprazolam. Blood glucose indices significantly reduced when fluoxetine was used in these two studies. These appear to be



the last studies to investigate the effect of fluoxetine or any other SSRIs on blood glucose levels in non-depressed diabetic patients.

### ***Effects of SSRI on regulating lipid profile***

The majority of research dealing with the influence of SSRI medications on lipid levels profiles was carried out among people suffering from psychiatric conditions, mostly depression (31). The studies showed that there are instances where these medications lead to elevated triglyceride, cholesterol and LDL levels. For instance, one study showed elevated blood cholesterol on fluoxetine while another found increased cholesterol, LDL, and triglycerides (32). Two other studies showed that paroxetine as well as venlafaxine have elevated LDL/cholesterol levels (33,34). Nevertheless, other studies fail to reveal major alterations of lipid profile attributed to the consumption of SSRI medications (35). In total, there are contradictions regarding the effects of SSRIs on the lipid profile and the results are not consistent.

Very few studies are available on the influence of SSRI drugs on lipid profiles in patients without psychopathology. In studies involving non-depressed diabetic patients, fluoxetine was the only medication investigated and shown to increase HDL (23) while decreasing blood triglycerides (26,27) without having any significant impact on total cholesterol (23,26,27).

According to studies, there are three key genes for liver carbohydrate metabolism; namely glucose-6 phosphatase catalytic subunit (G6PC), phosphoenolpyruvate carboxykinase (PEPCK) and glycogen synthase kinase 3 $\beta$  (GSK-3 $\beta$ ). A high level of such gluconeogenesis genes' increase in activity results in a disruption of the insulin signaling pathway which is mediated by AKT gene expression. It hence appears that fluoxetine could be controlling the activation of genes associated with the process of gluconeogenesis via regulation of the AKT gene present in the liver such that liver

glycogen synthesis would occur, insulin sensitivity would improve and blood glucose decrease (36).

It is important to acknowledge that patients with diabetes often have various health conditions, which require them to take many medications simultaneously (37). Additionally, incorporating a drug such as fluoxetine into their treatment plan will not replace the need for adherence to the primary medication used to lower blood sugar levels in these individuals (38). Thus, it appears that the addition of fluoxetine to the treatment plan for managing coexisting diabetes and obesity, in the absence of underlying depression, is currently unsupported and requires further investigation.

### **Serotonin and norepinephrine reuptake inhibitors (SNRIs)**

Duloxetine, Venlafaxine, Desvenlafaxine, Milnacipran, and Levomilnacipran are classified as selective serotonin and norepinephrine reuptake inhibitors (SNRIs) (39). The term SNRI was coined to describe drugs that suppress both neuronal serotonin (5-HT) and norepinephrine uptake transporters simultaneously. SNRIs, also known as dual reuptake inhibitors, are a kind of antidepressant that belongs to a larger functional family that includes TCAs (Tricyclic Antidepressants) like clomipramine and, to a lesser extent, imipramine and amitriptyline. What distinguishes SNRIs from TCAs is their lesser affinity for other receptors, including muscarinic, histaminergic, as well as adrenergic receptor medications (14,40-45).

Among these drugs, only the impact of duloxetine on the blood glucose levels and lipid profiles of diabetic individuals has been investigated. Researchers conducted studies from 2005 to 2007 to examine the impact of this medication on diabetic neuropathy, as well as its effects on blood glucose and cholesterol levels (40-45). Duloxetine was administered in these studies to alleviate neuropathic pain, while glucose and lipid levels were examined as a secondary measure to assess the safety of

this medication in diabetic patients. The subsequent findings indicated that this medication either had no impact on blood glucose (40,41,43) or substantially elevated blood sugar levels in diabetic individuals (42,44,45). However, in the majority of cases, there were no significant changes (40,41,45) or adverse alterations (42,44) in blood lipid markers related to blood fat.

In 2004, the FDA granted approval for the use of duloxetine in treating Major Depressive Disorder, and it subsequently became available for therapeutic purposes. Multiple pieces of data indicated that duloxetine and other SNRI medicines had a more rapid onset of pharmacological activity in the body and showed superior efficacy in responding to therapy compared to SSRI drugs. As a result, they were preferred for the treatment of major depression (39). Furthermore, duloxetine received approval as a therapeutic option for alleviating pain in individuals with diabetic neuropathy (46). A recently published systematic review highlights the favorable efficacy of this medication in managing painful diabetic neuropathy while also noting its minimal incidence of side effects. Nevertheless, the study did not address the impact of duloxetine on blood glucose and lipids in diabetic patients (47). Given that most studies have documented an increase in blood sugar levels and negative alterations in lipid profile as a result of Duloxetine, it is advisable to use greater caution while administering duloxetine for the treatment of diabetic neuropathy. Furthermore, further research is required, utilizing a larger sample size, to ascertain the true impact of this medication on blood sugar and lipid profiles in individuals with diabetes.

### Tricyclic antidepressant (TCA)

The medications belonging to this category include imipramine, desipramine, trimipramine, amitriptyline, nortriptyline, protriptyline, amoxapine, doxepin, maprotiline, and clomipramine (14). The TCAs block the transporter site for

norepinephrine and serotonin, thus increasing synaptic concentrations of these neurotransmitters. Secondary effects of the TCAs include antagonism at the muscarinic acetylcholine, histamine H1, and  $\alpha$ 1- and  $\alpha$ 2-adrenergic receptors. The potency of these effects on other receptors largely determines the side effect profile of these drugs causing a variety of adverse effects, including dry mouth, confusion, cognitive impairment, hypotension, orthostasis, blurred vision, urinary retention, drowsiness, and sedation (14,48).

None of these drugs have been tested on diabetic patients without psychiatric disorders to determine their effects on blood glucose and lipid levels. The inhibition of norepinephrine reuptake by TCA leads to the stimulation of glycogenolysis and gluconeogenesis (49). In addition, TCA inhibits the activity of muscarinic receptor 3 (M3) and alpha-adrenergic ( $\alpha$ -1AD) receptor, resulting in a decrease in insulin release and the development of hyperglycemia (50).

For instance, a cohort study with 23 non-T2D depressed patients, with 11 patients randomized to maprotiline and 12 patients assigned to fluoxetine, revealed that maprotiline led to an increase in body weight and a decrease in insulin sensitivity compared to fluoxetine (16,51). Thus, TCA maprotiline has a greater detrimental impact on glucose regulation compared to SSRI fluoxetine. In line with this discovery, TCA nortriptyline worsens the imbalance of glucose regulation in people with type 2 diabetes (52). Nevertheless, the SSRI fluoxetine has not been associated with harmful effects, but it is connected to symptomatic hypoglycemia (53).

### Conclusion

Lastly, the above review underscores the complex correlation between anti-depressant medications and metabolic effects on diabetes mellitus patients. Several studies suggest that SSRIs, especially fluoxetine improve hyperglycemia and insulin sensitivity, providing an alternative treatment approach.

However, the study of SNRIs and TCAs on the blood sugar and lipid profiles of diabetic patients has not been comprehensive enough to be relied upon. Thus, the findings underscore the need to consider the wider implications of antidepressants beyond their psychiatric indications. Fluoxetine has shown positive results, including weight loss and improved health, paving the way for a comprehensive approach to diabetes management in conjunction with mental health and metabolic parameters. Therefore, prospective studies examining the long-term consequences of antidepressants, particularly fluoxetine, on diabetic patients without depression should be the focus of future research. Moreover, randomized controlled trials investigating the safety and effectiveness of SNRIs and TCA on metabolic outcomes are required for a better understanding of metabolic implications. Additionally, more research should be conducted regarding the potential role of antidepressants as adjunct therapies specifically for obese type 2 diabetic patients. This approach will lead to better diabetes management, where treatment is tailored to on individual needs and expectations. In this regard, an integrated multi-disciplinary approach between psychiatric and diabetic support should inform

comprehensive recovery procedures. Incorporating the latest research into healthcare practice will assist health providers in implementing logical treatments aimed at enhancing the living situations of diabetic patients. This study offers recommendations for future research endeavors focused on addressing the incorporation of antidepressant usage in diabetes management, while emphasizing the need for careful attention.

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### **Conflict of Interest**

The authors declare no conflict of interest.

### **Authors' contributions**

Conceptualization, N.H. and M.A-A: Data gathering and curation, N.H., S.D, R.D. and F.S: Writing-original draft preparation, N.H. and S.D: Writing-review and final editing, N.H., S.D., R.D. and M.A-A: Supervision. All authors have read and agreed to the published version of the manuscript.

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