

RESEARCH

Open Access



Association of antidiabetic medications with psychiatric disorders in patients with type 2 diabetes: a cross-sectional study

Asieh Mansour¹, Athena Dehghan Najm Abadi², Farnaz Etesam³, Sara Danaei⁴, Yasaman Abaszadeh⁵, Farzaneh Torabi⁶, Asem Murshed⁷, Ensieh Nasli-Esfahani⁸, Zahra Vahabi^{9,10*} and Sayed Mahmoud Sajjadi-Jazi^{1*}

Abstract

Background Antihyperglycemic medications can affect more than just glucose control; they may also influence mental health outcomes. This study aimed to investigate the relationships between various antidiabetic medications and psychiatric disorders, including depression, anxiety, and sleep disturbances, in individuals with type 2 diabetes (T2DM).

Methods This cross-sectional study analyzed data from patients with T2DM, assessing psychiatric outcomes among these patients using various antidiabetic therapies. Sleep quality, anxiety, and depression were measured using validated scales, including the Pittsburgh Sleep Quality Index (PSQI), Generalized Anxiety Disorder-7 (GAD-7), and Patient Health Questionnaire-9 (PHQ-9), respectively.

Results This study involved 229 patients with a mean age $\pm$ standard deviation of 63.43 ± 10.38 years. The median body mass index (BMI) was 27.18 kg/m^2 , with an interquartile range (IQR) of $24.55\text{--}30.10$, and the median duration of diabetes was 11.00 years (IQR: $6.00\text{--}16.00$). The use of sodium glucose cotransporter-2 (SGLT-2) inhibitors was significantly associated with poorer sleep quality, as indicated by a higher odds ratio (odds ratio [OR] = 2.076, 95% confidence interval [CI]: $1.016\text{--}4.242$, $P = 0.045$). Insulin use was linked to increased anxiety, with an OR of 1.985 (95% CI: $1.007\text{--}3.913$, $P = 0.048$). In contrast, sulfonylureas and glinides were associated with lower odds of depression, with an OR of 0.374 (95% CI: $0.182\text{--}0.768$, $P = 0.007$). No significant associations were found between thiazolidinediones, metformin, or dipeptidyl peptidase-4 (DPP-4) inhibitors and any psychiatric outcomes.

Conclusion The use of SGLT2 inhibitors may negatively impact sleep quality, whereas insulin therapy is associated with increased anxiety symptoms. Conversely, sulfonylureas and glinides appear to have a protective effect against depression. These findings underscore the importance of considering psychiatric outcomes when prescribing antidiabetic medications.

*Correspondence:

Zahra Vahabi
zvahabi@sina.tums.ac.ir
Sayed Mahmoud Sajjadi-Jazi
mahmood.sajjadi@gmail.com

Full list of author information is available at the end of the article



© The Author(s) 2025. **Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

Introduction

Over the past several decades, the prevalence of diabetes, particularly type 2 diabetes (T2DM), has increased significantly due to factors such as unhealthy diets, physical inactivity, and an aging population. As diabetes and its complications, along with associated comorbidities, become more widespread, healthcare costs are rising substantially worldwide [1]. Therefore, it is crucial not only to manage blood sugar levels but also to address complications and comorbid conditions when treating patients with diabetes.

Psychiatric disorders, including depression, anxiety, and sleep disorders, are linked to a higher risk of developing T2DM. A meta-analysis of 245 studies revealed an elevated prevalence of T2DM, with rates of 40% among individuals with sleep disorders, 14% among those with anxiety, and 9% among those with depression [2]. Possible explanations include the side effects of antipsychotic and mood-stabilizing medications, as well as unhealthy lifestyle factors [3, 4].

Patients with diabetes are treated with a variety of oral antidiabetic drugs (OADs), such as metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium glucose cotransporter-2 (SGLT-2) inhibitors, α -glucosidase inhibitors, sulfonylureas, thiazolidinediones, and insulin or combination therapies. The choice of medication is influenced by individual patient factors, the severity of the disease, blood glucose levels, and the risk of complications [5, 6]. Evidence suggests that antihyperglycemic medications may have effects that extend beyond glucose control, particularly regarding mental health and sleep regulation. These medications can either increase the risk of depression, anxiety, and sleep disturbances or provide potential benefits in alleviating these conditions, depending on the specific drug and individual patient factors [6–9]. This cross-sectional study aimed to investigate whether individual antihyperglycemic medications affect common psychiatric disorders, including depressive disorder, anxiety disorder, and sleep disorder, in patients with T2DM.

Methods

Enrollment took place at the diabetes clinic within the Endocrinology and Metabolism Research Center (Tehran University of Medical Sciences, Tehran, Iran). Men and women aged 18 years and older with T2DM, as defined by the 1999 World Health Organization (WHO) criteria [10], were eligible to participate. Exclusion criteria included current pregnancy and individuals with severe cognitive or neurological disorders, such as stroke, dementia, or traumatic brain injury.

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Review

Board of Tehran University of Medical Sciences (IR.TUMS.EMRI.REC.1401.042), and all participants provided written informed consent.

Clinical and laboratory data

Laboratory test results were obtained from the clinic's laboratory information system after receiving approval from the Ethics Committee. Data were collected through in-person interviews. Patients' height was measured to the nearest 0.1 cm, and their weight was recorded to the nearest 0.1 kg. The Body Mass Index (BMI) was then calculated by dividing weight in kilograms by the square of height in meters. Smoking was defined as consistent cigarette use over the past six months. Alcohol consumption was defined as an average daily intake of more than 20 g over the previous year. Blood pressure was measured on the left arm after a minimum 10-min rest period in a seated position. Hypertension was defined as a blood pressure of $\geq 130/80$ mmHg or the use of antihypertensive medications, including beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), calcium channel blockers, or diuretics [11]. Combination antidiabetic therapy was defined as the concurrent use of two or more antidiabetic drugs.

Mental health and sleep assessment

The identification of individuals at risk for mental health issues and sleep disturbances was conducted using well-established self-report questionnaires. The Patient Health Questionnaire-9 (PHQ-9), with a score range of 0–27, assessed depressive symptoms. The Generalized Anxiety Disorder-7 (GAD-7), with a score range of 0–21, measured anxiety severity. Sleep quality was evaluated using the Pittsburgh Sleep Quality Index (PSQI), which has a score range of 0–21 and assesses various sleep-related factors, including duration, disturbances, and overall sleep efficiency. Higher scores on all three scales indicate greater symptom severity [12–14].

Sample size

Based on a study by Kant et al. [15], the reported prevalence of depression in patients with T2DM was 49.2%. The sample size was calculated using the formula provided below, with a margin of error of 7% and a confidence interval (CI) of 95% for proportion estimation. The initial calculation yielded a sample size of 196 participants. Accounting for a potential attrition rate of 15%, the final sample size was determined to be 231 participants.

$$n = \frac{Z^2 \times P \times (1 - P)}{d^2}$$

Statistical analysis

All statistical analyses were conducted using SPSS software version 26.0 (IBM Corp., Armonk, NY, USA). The normality of the data was assessed using the Shapiro–Wilk test. Quantitative variables with a normal distribution were reported as mean $\pm$ standard deviation (SD), while skewed data were presented as median with interquartile range (IQR). Numbers (%) were used to summarize categorical variables. A univariate and multivariate regression models were employed to examine the relationship between antidiabetic medications and depression, anxiety, and sleep disturbances, using the following adjustment models: Model 1: Unadjusted (crude) model, Model 2: Adjusted for age and sex, Model 3: Adjusted for all variables in Model 2 plus alcohol consumption, smoking, Hemoglobin A1c (HbA1C), BMI, duration of diabetes, marital status, psychiatric medication use, hypertension, and combination antidiabetic therapy. The results are presented as odds ratios (OR) with 95% CI. A *p*-value of <0.05 was considered statistically significant.

Results

From January to December 2023, a total of 239 individuals with T2DM met the inclusion criteria. Of those, 229 patients were included in the final analysis, consisting of 101 men and 128 women. Table 1 summarizes the baseline characteristics of the study population, stratified by sex. The mean age $\pm$ SD was 64.21 ± 10.96 years for males and 62.81 ± 9.88 years for females; this difference was not statistically significant ($P=0.229$). Similarly, the duration of diabetes was comparable between the two groups ($P=0.133$). However, smoking ($P=0.002$) and alcohol consumption ($P=0.007$) were significantly more prevalent among males than females. Furthermore, a significantly higher percentage of males were married (86.1%) compared to females (67.2%; $P<0.001$).

Metabolic and laboratory parameters

A significant difference in median BMI was found between females and males ($P=0.005$), with females exhibiting a higher median BMI of 28.08 kg/m^2 (IQR: 24.77–31.91) compared to 26.21 kg/m^2 (IQR: 24.33–28.10) in males.

Fasting blood glucose (FBS) and HbA1c levels did not differ significantly between the two groups ($p>0.05$). The liver enzyme alanine aminotransferase (ALT) was significantly lower in females compared to males ($P=0.01$). Additionally, high-density lipoprotein cholesterol (HDL-C) level was significantly higher in females ($P=0.002$), while total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglyceride levels showed no significant differences between the groups. The median

serum creatinine level was significantly lower in females, at 0.88 mg/dL (IQR: 0.74–1.07), compared to males, who had a median level of 1.00 mg/dL (IQR: 0.89–1.2) ($P<0.001$). Conversely, the estimated glomerular filtration rate (eGFR) was significantly lower in females ($P=0.002$). The prevalence of hypertension was high in both males (91.1%) and females (87.5%), but the difference was not statistically significant ($P=0.387$).

Diabetes treatment and medication use

Patients in this study used the following antidiabetic medications: metformin (82.1%), sulfonylureas/glinides (23.6%), insulin (36.7%), DPP-4 inhibitors (35.4%), SGLT2 inhibitors (28.8%), and thiazolidinediones (2.6%). Alpha-glucosidase inhibitors were rarely used (less than 0.5%). No patients received Glucagon-like peptide-1 (GLP-1) receptor agonists. Furthermore, 70.7% of individuals were on a combination antidiabetic regimen, and 16.2% were prescribed psychiatric medications.

Table 1 provides a detailed list of the medications used by patients, according to their sex. Sulfonylureas and glinides were prescribed more frequently in males than females ($P=0.024$). There were no significant sex differences in the use of SGLT2 inhibitors, metformin, or DPP-4 inhibitors. Although a higher proportion of females (40.6%) than males (31.7%) were prescribed insulin, this difference was not statistically significant ($P=0.163$).

Psychological and sleep parameters

The median (IQR) GAD-7 anxiety score was significantly higher in females, at 11.00 (4.00–15.75), compared to males, at 6.00 (3.00–12.50) ($P=0.002$). In contrast, PHQ-9 depression scores and PSQI sleep quality scores did not significantly differ between males and females ($P>0.05$).

Table 2 presents the associations between different antidiabetic medications and mental health outcomes, including depression (PHQ-9), anxiety (GAD-7), and sleep quality (PSQI), across three models. In Model 3, SGLT2 inhibitors showed no significant association with PHQ-9 (OR=0.846, 95% CI: 0.424–1.691, $P=0.636$) or GAD-7 (OR=0.637, 95% CI: 0.313–1.296, $P=0.213$). However, a significant positive association was observed with PSQI (OR=2.076, 95% CI: 1.016–4.242, $P=0.045$), suggesting a potential link between SGLT2 inhibitors and reduced sleep quality.

Insulin use was significantly associated with higher odds of depression in both Model 1 (OR=2.535, 95% CI: 1.427–4.502, $P=0.002$) and Model 2 (OR=2.470, 95% CI: 1.387–4.401, $P=0.002$). However, this association was not significant in Model 3 ($P=0.053$). A significant association was observed between insulin use and GAD-7 in

Table 1 Baseline characteristics of patients stratified by sex

Characteristics	Male (n = 101)	Female (n = 128)	P-value
Age (years) ^a	64.21 ± 10.96	62.81 ± 9.88	0.229
Diabetes duration (years) ^b	10.00 (6.00–14.00)	11.00 (6.00–17.75)	0.133
Smoking, current (yes) ^c	17.00 (16.80)	6.00 (4.70)	0.002
Alcohol, current (yes) ^c	14.00 (13.90)	5.00 (3.90)	0.007
Marriage (yes) ^c	87.00 (86.10)	86.00 (67.20)	< 0.001
BMI (kg/m ²) ^b	26.21 (24.33–28.10)	28.08 (24.77–31.91)	0.005
FBS (mg/dL) ^b	139.00 (111.75–206.00)	144.00 (115.00–200.00)	0.858
HbA1c (%) ^b	7.60 (6.90–9.01)	7.30 (6.70–8.50)	0.205
AST (U/L) ^b	21.00 (17.00–25.00)	19.00 (16.00–23.00)	0.097
ALT (U/L) ^b	22.00 (16.00–29.00)	19.00 (14.00–24.00)	0.01
Total cholesterol (mg/dL) ^b	131.00 (111.00–151.00)	137.00 (117.00–155.50)	0.103
HDL-C (mg/dL) ^b	39.00 (34.50–44.00)	42.00 (36.25–51.75)	0.002
LDL-C (mg/dL) ^b	65.00 (53.00–86.00)	72.00 (59.00–86.00)	0.087
Triglycerides (mg/dL) ^b	120.00 (93.75–148.00)	123.00 (99.00–171.00)	0.052
TSH (uIU/mL) ^b	1.62 (1.08–2.11)	1.65 (1.18–2.42)	0.509
Creatinine (mg/dL) ^b	1.00 (0.89–1.2)	0.88 (0.74–1.07)	< 0.001
eGFR (mL/min/1.73m ²) ^a	82.99 ± 21.75	73.38 ± 22.67	0.002
HTN (yes) ^c	92.00 (91.10)	112.00 (87.50)	0.387
SGLT2 inhibitors (yes) ^c	23.00 (22.80)	43.00 (33.60)	0.073
Sulfonylureas and glinides (yes) ^c	31.00 (30.70)	23.00 (18.00)	0.024
Insulin injection (yes) ^c	32.00 (31.70)	52.00 (40.60)	0.163
Thiazolidinediones (yes) ^c	3.00 (3.00)	3.00 (2.30)	0.768
Metformin (yes) ^c	82.00 (81.20)	106 (82.80)	0.750
DPP-4 inhibitors (yes) ^c	33.00 (32.70)	48.00 (37.50)	0.448
Alpha-glucosidase inhibitor (yes) ^d	0.00 (0.00)	1.00 (0.80)	1.000
Combination antidiabetic therapy (yes) ^c	66.00 (65.30)	96.00 (75.00)	0.111
Psychiatric drugs (yes) ^c	17.00 (16.80)	20 (15.60)	0.805
PHQ-9 scores ^b	11.00 (5.00–14.50)	12.00 (6.00–16.75)	0.062
GAD-7 scores ^b	6.00 (3.00–12.50)	11.00 (4.00–15.75)	0.002
PSQI scores ^b	5.00 (3.00–9.00)	6.00 (4.00–11.00)	0.314

Data are presented as mean ± SD, median (IQR) or number (%)

BMI body mass index, *FBS* fasting blood sugar, *HbA1c* hemoglobinA1c, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *TSH* thyroid-stimulating hormone, *eGFR* estimated glomerular filtration rate, *HTN* hypertension, *SGLT2* sodium-glucose cotransporter-2, *DPP-4* dipeptidyl peptidase 4, *PHQ-9* patient health questionnaire-9, *GAD-7* generalized anxiety disorder assessment, *PSQI* pittsburg sleep quality index

^a Independent sample t-test

^b Mann-Whitney U test

^c Chi-square test

^d Fisher's exact test

Model 1 (OR = 1.834, 95% CI: 1.065–3.159, P = 0.029) and Model 3 (OR = 1.985, 95% CI: 1.007–3.913, P = 0.048). Additionally, insulin use was also significantly associated with PSQI in Model 1 (OR = 1.864, 95% CI: 1.058–3.284, P = 0.031) and Model 2 (OR = 1.855, 95% CI: 1.047–3.287, P = 0.034), but this association became non-significant in Model 3 (P = 0.180).

Thiazolidinediones, metformin, and DPP-4 inhibitors were not significantly associated with PHQ-9, GAD-7, or PSQI in any model. Sulfonylureas and glinides were

significantly associated with lower odds of depression (PHQ-9) in Model 1 (OR = 0.406, 95% CI: 0.218–0.758, P = 0.005), Model 2 (OR = 0.424, 95% CI: 0.225–0.800, P = 0.008), and Model 3 (OR = 0.374, 95% CI: 0.182–0.768, P = 0.007). However, no significant associations were observed with GAD-7 or PSQI.

Table 2 Association between antidiabetic medications with depression, anxiety and sleeping disturbances using logistic regression analysis (sample size n = 229)

Variable	PHQ-9			GAD-7			PSQI		
	OR	0.95% CI	P value	OR	0.95% CI	P value	OR	0.95% CI	P value
SGLT2 inhibitors									
Model 1 (unadjusted)	0.838	0.471–1.490	0.546	0.991	0.557–1.762	0.974	2.217	1.189–4.135	0.012
Model 2	0.809	0.451–1.452	0.478	0.866	0.477–1.574	0.638	2.123	1.132–3.981	0.019
Model 3	0.846	0.424–1.691	0.636	0.637	0.313–1.296	0.213	2.076	1.016–4.242	0.045
Insulin injection									
Model 1 (unadjusted)	2.535	1.427–4.502	0.002	1.834	1.065–3.159	0.029	1.864	1.058–3.284	0.031
Model 2	2.470	1.387–4.401	0.002	1.748	1.00–3.054	0.050	1.855	1.047–3.287	0.034
Model 3	1.940	0.993–3.793	0.053	1.985	1.007–3.913	0.048	1.574	0.811–3.053	0.180
Thiazolidinediones									
Model 1 (unadjusted)	0.729	0.144–3.690	0.702	2.598	0.466–14.478	0.276	1.353	0.243–7.545	0.730
Model 2	0.804	0.153–4.212	0.796	2.820	0.471–16.878	0.256	1.220	0.212–7.029	0.824
Model 3	1.020	0.182–5.713	0.982	2.505	0.379–16.574	0.341	1.041	0.172–6.284	0.965
Metformin									
Model 1 (unadjusted)	1.373	0.697–2.704	0.359	1.895	0.925–3.884	0.081	0.731	0.360–1.484	0.386
Model 2	1.371	0.694–2.709	0.363	1.901	0.912–3.963	0.086	0.718	0.352–1.462	0.361
Model 3	1.789	0.815–3.928	0.147	2.001	0.878–4.557	0.099	0.547	0.244–1.227	0.144
DPP4 inhibitors									
Model 1 (unadjusted)	0.750	0.434–1.296	0.303	1.104	0.640–1.903	0.723	1.131	0.649–1.970	0.664
Model 2	0.736	0.425–1.275	0.274	1.057	0.604–1.849	0.846	1.113	0.637–1.945	0.706
Model 3	0.636	0.328–1.234	0.181	0.880	0.455–1.704	0.705	0.961	0.501–1.843	0.904
Sulfonylureas and glinides									
Model 1 (unadjusted)	0.406	0.218–0.758	0.005	0.554	0.293–1.050	0.070	0.652	0.352–1.206	0.173
Model 2	0.424	0.225–0.800	0.008	0.617	0.319–1.196	0.153	0.655	0.349–1.229	0.187
Model 3	0.374	0.182–0.768	0.007	0.505	0.238–1.071	0.075	0.524	0.260–1.057	0.071

Model 2 includes variables from model 1 plus age and sex; Model 3 includes variables from model 2 plus alcohol consumption, smoking, HbA1c, BMI, diabetes duration, marital status, psychiatric drugs, hypertension, combination antidiabetic therapy

PHQ-9 patient health questionnaire-9, GAD-7 generalized anxiety disorder assessment, PSQI pittsburg sleep quality index, SGLT2 sodium-glucose cotransporter-2, DPP-4 dipeptidyl peptidase 4, BMI body mass index, HbA1c hemoglobinA1c, OR odds ratio, CI confidence interval

Discussion

SGLT2 inhibitors were associated with poorer sleep quality, whereas insulin use was linked to increased anxiety. In contrast, sulfonylureas and glinides were associated with a lower risk of depression. The use of thiazolidinediones, metformin, or DPP-4 inhibitors was not significantly associated with psychiatric disorders, including depression, anxiety, and sleep disturbances.

SGLT2 inhibitors have complex effects on sleep quality, potentially causing nocturia-related disruptions but also offering benefits by reducing fluid shifts and improving respiratory function during sleep [16, 17]. Additionally, several studies have highlighted the potential benefits of SGLT2 inhibitors in patients with obstructive sleep apnea (OSA), as they target key mechanisms involved in its pathogenesis, such as weight reduction and improved glycemic control. These effects suggest that SGLT2 inhibitors may play a role in mitigating the severity of OSA [18, 19]. However, a meta-analysis evaluating their

impact on sleep-disordered breathing found that while SGLT2 inhibitors significantly improved HbA1c levels, they did not lead to a statistically significant improvement in apnea severity, as measured by the apnea-hypopnea index (AHI) or in oxygen saturation (SpO2) levels [8].

The effects of SGLT2 inhibitors on sleep quality have been reported with varying findings. One study found no significant impact on sleep quality, as assessed by the PSQI, but noted improvements in overall quality of life. However, this study also observed a significant increase in both nocturia and daytime urination frequency [20]. A more recent study similarly found that SGLT2 inhibitors did not significantly affect sleep quality or daytime sleepiness, as measured by the Epworth Sleepiness Scale. Although voiding volumes increased, there was no significant change in nocturia or daytime urination frequency, and lower urinary tract symptoms (LUTS) remained stable [16]. In contrast, another study investigating

insomnia and sleep duration found that SGLT2 inhibition was associated with a 20.9% reduction in the odds of insomnia and a positive correlation with sleep duration (β coefficient=0.186), indicating a potential role in improving sleep patterns [21]. Additionally, switching to tofogliflozin, which has a shorter half-life than other SGLT2 inhibitors, was associated with a significant reduction in nocturnal urination frequency, with 33% of participants reporting improved sleep quality [22].

Our findings suggest a potential link between the use of SGLT2 inhibitors and worsening sleep, possibly due to an increase in nocturia. SGLT2 inhibitors can induce LUTS [23], including increased urinary frequency, urgency, polyuria, and nocturia, as a result of their mechanism promoting natriuresis and osmotic diuresis. These effects are more pronounced in individuals with diabetes, particularly those with poor metabolic control or autonomic neuropathy, and can significantly impact quality of life by disrupting sleep and daily activities. While LUTS associated with SGLT2 inhibitors are generally mild and transient, resolving within days to weeks, some patients, especially older adults or those with preexisting LUTS, may experience persistent symptoms [24]. LUTS, including nocturia, can substantially affect quality of life by disrupting sleep and causing daytime fatigue, especially in older adults [25].

Strategies such as optimizing dosing schedules [26] or selecting an SGLT2 inhibitor with a shorter half-life [22] could help mitigate any negative effects on sleep quality for patients undergoing SGLT2 inhibitor therapy. In addition, SGLT2 inhibitors may impair sleep quality by exacerbating nocturia, particularly when co-administered with diuretics [27]. In our analysis, we accounted for hypertension as a potential confounder by incorporating diuretic use into the hypertension adjustment, thereby better isolating the independent effects of SGLT2 inhibitors.

Our research revealed a significant link between insulin use and elevated anxiety levels, as measured by GAD-7 scores. Contrary to our results, insulin treatment in rodent models has been shown to alleviate anxiety-like behaviors through various mechanisms. For example, in streptozotocin-induced diabetic mice, a model that mimics type 1 diabetes, insulin treatment restored neurotransmitter balance (gamma-aminobutyric acid [GABA], serotonin, dopamine) and modulated the hypothalamic–pituitary–adrenal (HPA) axis, leading to a reduction in anxiety-like behaviors [28]. Likewise, intranasal insulin treatment significantly alleviated methamphetamine-induced anxiety-like behavior in rats by reducing neuroinflammation and lowering pro-inflammatory markers in the hippocampus [29]. Human studies, however, reveal a more intricate relationship, suggesting that anxiety

in insulin users is not solely determined by biological mechanisms, but also influenced by psychological factors. Psychological insulin resistance (PIR), is a common condition in T2DM patients, with many of them experiencing anxiety about starting or intensifying insulin therapy due to fears of hypoglycemia, perceived stigma, and concerns about treatment burden. One study found that 82% of patients initially refused insulin, citing psychological barriers, with fear of hypoglycemia being the most significant concern, while fear of injections was less prominent [30]. Another study reported that 30–50% of patients experienced anxiety related to injection pain [31]. Negative attitudes toward insulin therapy were three times more common than positive ones, often linked to technical concerns (pain, hypoglycemia, weight gain) and experiential concerns (perceived disease progression or failure of prior treatments), as well as misconceptions about insulin's effects [32]. Despite the importance of injectable therapies like GLP-1 receptor agonists or insulin for long-term diabetes management, anxiety related to injections remains a significant barrier to treatment adherence in these patients [31].

Individuals with T2DM are at increased risk for depression [33]. While the potential effects of antidiabetic medications used to manage T2DM on depression risk have been studied [34], the overall impact of these medications on mental health outcomes, particularly depression, remains unclear. A large population-based cohort study by Wahlqvist et al. reported that individuals with T2DM who were not receiving oral antidiabetic treatment had a 2.62-fold increased risk of developing affective disorders compared to non-diabetic individuals. Interestingly, patients treated with a combination of sulfonylureas and metformin showed a 60% lower risk of affective disorders compared to those who were untreated, suggesting that this combination therapy may offer a protective effect against depression [35]. Supporting this observation, our results revealed an association between the intake of sulfonylureas and glinides and a decreased risk of depression. Further evidence comes from a preclinical study in mice, where 12 weeks of chronic unpredictable mild stress (CUMS) caused depressive-like behaviors and insulin resistance. Notably, glyburide treatment reversed these effects, leading to improved behavioral performance, alleviation of insulin intolerance, and enhanced insulin signaling in the hippocampus. These beneficial effects were linked to glyburide's ability to block the activation of the NOD-like receptor protein 3 (NLRP3) inflammasome [36].

However, the relationship between sulfonylureas and the risk of depression is not entirely consistent across studies. A retrospective cohort study conducted among Japanese patients with T2DM found no significant

association between sulfonylurea use and the risk of developing depression. This study adjusted for potential confounding factors, such as age, sex, HbA1c levels, and medical history, suggesting that sulfonylureas neither increase nor decrease the risk of depression in these patients [6]. On the other hand, a large population-based cohort study conducted by Wium-Andersen et al. indicated that while metformin, DPP-4 inhibitors, GLP-1 analogs, and SGLT2 inhibitors were associated with a lower risk of depression, the use of insulin and sulfonylureas was linked to higher odds of developing depression [7]. This finding aligns with results from another extensive study comparing various oral hypoglycemic agents, which found that sulfonylureas were associated with a slightly higher risk of depression compared to metformin [37] with females being more affected than males [5].

Several limitations should be acknowledged. The cross-sectional design restricts the ability to establish causal relationships between antidiabetic medications and psychiatric outcomes, highlighting the need for longitudinal studies. Additionally, reliance on self-reported measures for sleep quality, depression, and anxiety may introduce bias, as these assessments, despite being validated and reliable, do not provide definitive clinical diagnoses. Furthermore, since the study population was drawn from a single diabetes clinic, the generalizability of the findings is limited. Further research is needed to confirm these results in other populations.

Conclusion

Our study highlights the potential psychiatric implications of antidiabetic medications in patients with T2DM. SGLT2 inhibitors were associated with poorer sleep quality, while insulin use correlated with higher anxiety symptoms. In contrast, sulfonylureas and glinides appeared to be linked to a lower risk of depression. These findings emphasize the need for a personalized approach to diabetes management, considering both metabolic and mental health aspects. Further studies are needed to explore the underlying mechanisms and develop strategies to mitigate these negative effects, ultimately enhancing patient-centered diabetes care.

Acknowledgements

We are thankful to the patients who participated in the study.

Author contributions

AM Analysis and interpretation of data, Drafting of manuscript, Critical revision, ADNA Study conception and design, Acquisition of data, SD Acquisition of data, YA Acquisition of data, FT Acquisition of data, FE Critical revision, AM Critical revision, ENE Acquisition of data, ZV Study conception and design, Critical revision, SMSJ Study conception and design, Analysis and interpretation of data, Critical revision. All authors have read and approved the manuscript.

Funding

No funding to declare.

Availability of data and materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Review Board of Tehran University of Medical Sciences (IR.TUMS.EMRI.REC.1401.042). All participants provided written informed consent.

Consent for publication

Not applicable.

Competing interests

None of the authors have any competing of interest or financial ties to disclose.

Author details

¹Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran. ²Clinical Psychology and Family Research Institute, Shahid Beheshti University, Tehran, Iran. ³Psychosomatic Medicine Research Center, Department of Psychiatry, Tehran University of Medical Sciences, Tehran, Iran. ⁴Student Research Committee, Hamadan University of Medical Sciences, Hamadan, Iran. ⁵Department of Physiology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran. ⁶Department of Health Psychology, School of Behavioral Sciences and Mental Health, Iran University of Medical Sciences, Tehran, Iran. ⁷Department of General Internal Medicine, Royal Alexandra Hospital, Edmonton, Canada. ⁸Diabetes Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran. ⁹Cognitive Neurology, Dementia and Neuropsychiatry Research Center, Tehran University of Medical Sciences, Tehran, Iran. ¹⁰Department of Geriatric, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.

Received: 1 June 2025 Accepted: 28 June 2025

Published online: 22 July 2025

References

- Saijo Y, Okada H, Hata S, Nakajima H, Kitagawa N, Okamura T, et al. Reasons for discontinuing treatment with sodium-glucose cotransporter 2 inhibitors in patients with diabetes in real-world settings: the KAMOGAWA-A study. *J Clin Med*. 2023;12(22):6993.
- Lindekilde N, Scheuer SH, Rutters F, Knudsen L, Lasgaard M, Rubin KH, et al. Prevalence of type 2 diabetes in psychiatric disorders: an umbrella review with meta-analysis of 245 observational studies from 32 systematic reviews. *Diabetologia*. 2022;65(3):440–56.
- Lee M-K, Lee S-Y, Sohn S-Y, Ahn J, Han K, Lee J-H. Type 2 diabetes and its association with psychiatric disorders in young adults in South Korea. *JAMA Netw Open*. 2023;6(6):e2319132.
- Altuwairqi YA. Prevalence and major risk factors of type 2 diabetes mellitus among adult psychiatric patients in Taif Mental Hospital in Saudi Arabia. *SAS J Med*. 2024;3:156–61.
- Pawaskar MD, Anderson RT, Balkrishnan R. Self-reported predictors of depressive symptomatology in an elderly population with type 2 diabetes mellitus: a prospective cohort study. *Health Qual Life Outcomes*. 2007;5:1–6.
- Akimoto H, Tezuka K, Nishida Y, Nakayama T, Takahashi Y, Asai S. Association between use of oral hypoglycemic agents in Japanese patients with type 2 diabetes mellitus and risk of depression: a retrospective cohort study. *Pharmacol Res Perspect*. 2019;7(6):e00536.
- Wium-Andersen IK, Osler M, Jørgensen MB, Rungby J, Wium-Andersen MK. Diabetes, antidiabetic medications and risk of depression—a population-based cohort and nested case-control study. *Psychoneuroendocrinology*. 2022;140: 105715.

8. Mir T, Atique HB, Regmi N, Sattar Y, Sundus S, Ambreen S, et al. SGLT2 inhibitors and sleep apnea; how helpful are the medications: a meta-analysis. *Endocrine Metab Sci*. 2021;2: 100084.
9. Sarkaki A, Farbood Y, Badavi M, Khalaj L, Khodaghali F, Ashabi G. Metformin improves anxiety-like behaviors through AMPK-dependent regulation of autophagy following transient forebrain ischemia. *Metab Brain Dis*. 2015;30:1139–50.
10. Alberti KGMM, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. *Diabet Med*. 1998;15(7):539–53.
11. Flack JM, Adekola B. Blood pressure and the new ACC/AHA hypertension guidelines. *Trends Cardiovasc Med*. 2020;30(3):160–4.
12. Farrahi Moghaddam J, Nakhaee N, Sheibani V, Garrusi B, Amirakafi A. Reliability and validity of the Persian version of the Pittsburgh Sleep Quality Index (PSQI-P). *Sleep Breath*. 2012;16:79–82.
13. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(9):606–13.
14. Thour A, Nagra R, Gosal A, Sehrawat T, Das S, Gupta Y. Anxiety among patients with diabetes mellitus evaluated using generalized anxiety disorder 7-item scale. *J Soc Health Diabetes*. 2016;4(02):133–6.
15. Kant R, Yadav P, Barnwal S, Dhiman V, Abraham B, Gawande K. Prevalence and predictors of depression in type 2 diabetes mellitus. *J Educ Health Promot*. 2021;10:352.
16. Semiz GG, Sarıkaya E, Arayıcı ME, Bozkurt O, Yener S, Demir T. Do sodium glucose co-transporter-2 (sglt-2) inhibitors affect lower urinary tract, sleep and quality of life in people with type 2 diabetes? *J Basic Clin Health Sci*. 2021;8(3):660–7.
17. Huang L, Feng T. The application of GLP-1 receptor agonists and SGLT2 inhibitors in obstructive sleep apnea: breakthrough or overhyped? *Exploratory Res Hypothesis Med*. 2025;10(2):143–5.
18. Tanriover C, Ucku D, Akyol M, Cevik E, Kanbay A, Sridhar VS, et al. Potential use of SGLT-2 inhibitors in obstructive sleep apnea: a new treatment on the horizon. *Sleep Breath*. 2023;27(1):77–89.
19. Monda VM, Gentile S, Porcellati F, Satta E, Fucili A, Monesi M, et al. Heart failure with preserved ejection fraction and obstructive sleep apnea: a novel paradigm for additional cardiovascular benefit of SGLT2 inhibitors in subjects with or without type 2 diabetes. *Adv Ther*. 2022;39(11):4837–46.
20. Şahin S, Haliloğlu Ö, Korkmaz ÖP, Durcan E, Şahin HR, Yumuk VD, et al. Does treatment with sodium-glucose co-transporter-2 inhibitors have an effect on sleep quality, quality of life, and anxiety levels in people with type 2 diabetes mellitus? *Turk J Med Sci*. 2021;51(2):735–42.
21. Luo J, Tu L, Zhou C, Li G, Shi L, Hu S. SGLT2 inhibition, circulating proteins, and insomnia: a mendelian randomization study. *Sleep Med*. 2024;119:480–7.
22. Inoue S, Yasuda H, Yoshida K, Mori K, Ogawa K, Yokotsuka Y, et al. Effects of switching from another sodium-glucose cotransporter 2 inhibitor to tofogliflozin on nocturia in patients with type 2 diabetes. *Cureus*. 2024;16(4):e59411.
23. Chilelli NC, Bax G, Bonaldo G, Ragazzi E, Iafraite M, Zattoni F, et al. Lower urinary tract symptoms (LUTS) in males with type 2 diabetes recently treated with SGLT2 inhibitors—overlooked and overwhelming? A retrospective case series. *Endocrine*. 2018;59:690–3.
24. Gorgojo-Martínez JJ, Górriz JL, Cebrián-Cuenca A, Castro Conde A, Velasco AM. Clinical recommendations for managing genitourinary adverse effects in patients treated with SGLT-2 inhibitors: a multidisciplinary expert consensus. *J Clin Med*. 2024;13(21):6509.
25. Kim S-O, Choi HS, Kim YJ, Kim HS, Hwang IS, Hwang EC, et al. Impact of nocturia on health-related quality of life and medical outcomes study sleep score in men. *Int Neurourol J*. 2011;15(2):82.
26. Ferrannini E, Ramos SJ, Salsali A, Tang W, List JF. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase 3 trial. *Diabetes Care*. 2010;33(10):2217–24.
27. Krepostman N, Kramer H. Lower urinary tract symptoms should be queried when initiating sodium glucose co-transporter 2 inhibitors. *Kidney360*. 2021;2(4):751–4.
28. Gupta D, Radhakrishnan M, Kurhe Y. Insulin reverses anxiety-like behavior evoked by streptozotocin-induced diabetes in mice. *Metab Brain Dis*. 2014;29:737–46.
29. Beirami E, Oryan S, Tamijani SMS, Ahmadiani A, Dargahi L. Intranasal insulin treatment alleviates methamphetamine induced anxiety-like behavior and neuroinflammation. *Neurosci Lett*. 2017;660:122–9.
30. Petrak F, Herpertz S, Stridde E, Pfützner A. Psychological insulin resistance in type 2 diabetes patients regarding oral antidiabetes treatment, subcutaneous insulin injections, or inhaled insulin. *Diabetes Technol Ther*. 2013;15(8):702–10.
31. Kruger DF, LaRue S, Estepa P. Recognition of and steps to mitigate anxiety and fear of pain in injectable diabetes treatment. *Diabetes Metab Syndr Obes Targets Ther*. 2015;8:49–56.
32. Hunt LM, Valenzuela MA, Pugh JA. NIDDM patients' fears and hopes about insulin therapy: the basis of patient reluctance. *Diabetes Care*. 1997;20(3):292–8.
33. Nouwen A, Winkley K, Twisk J, Lloyd CE, Peyrot M, Ismail K, et al. Type 2 diabetes mellitus as a risk factor for the onset of depression: a systematic review and meta-analysis. *Diabetologia*. 2010;53:2480–6.
34. Ganz M, Schrier R, Yomtov N, Spivak M, Bulmash M, Appelbaum Y, et al. Investigating the influence of antidiabetic medications and psychosocial factors. *Cureus*. 2024;16(5):e60270.
35. Wahlqvist ML, Lee M-S, Chuang S-Y, Hsu C-C, Tsai H-N, Yu S-H, et al. Increased risk of affective disorders in type 2 diabetes is minimized by sulfonylurea and metformin combination: a population-based cohort study. *BMC Med*. 2012;10:1–13.
36. Su W-J, Peng W, Gong H, Liu Y-Z, Zhang Y, Lian Y-J, et al. Antidiabetic drug glyburide modulates depressive-like behavior comorbid with insulin resistance. *J Neuroinflammation*. 2017;14:1–12.
37. Yu H, Yang R, Wu J, Wang S, Qin X, Wu T, et al. Association of metformin and depression in patients with type 2 diabetes. *J Affect Disord*. 2022;318:380–5.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.