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Short Term Risk of Type 2 Diabetes in Patients Using Various Antidepressants Compared with Patients Using Fluoxetine

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ABSTRACT

Background: The objective is to compare the risk of developing type 2 diabetes (T2D) within a year in patients prescribed various antidepressants (ADs) and those prescribed fluoxetine as a control group.
Methods: This study used standardized data from the Health Insurance Review and Assessment Service claims database (n = 1,456,489). Patients aged ≥10 years with no previous use of ADs and no history of diabetes mellitus, regardless of whether they were diagnosed with any depressive disorder, were eligible for this study. Among these eligible patients, those who had used ADs for the first time or had never used them between January 2017 and December 2017 were selected for this study. I compared the short-term (<12 months) risk of T2D in patients using various ADs, excluding tricyclic ADs, with those using fluoxetine as a control. The Cox proportional hazards model was used to calculate hazard ratios (HRs).
Results: The HRs (95% confidence intervals) for T2D incidence in the various AD groups compared with that in the fluoxetine group are as follows: 0.84 (0.67-1.06, *P* = .15), bupropion; 0.91 (0.77-1.07, *P* = .25), tianeptine; 0.91 (0.77-1.07, *P* = .25), escitalopram; 0.96 (0.82-1.13, *P* = .63), paroxetine; 0.97 (0.70-1.35, *P* = .87), fluvoxamine; 1.07 (0.85-1.36, *P* = .55), vortioxetine; 1.07 (0.91-1.25, *P* = .42), sertraline; 1.14 (0.99-1.31, *P* = .07), duloxetine; 1.17 (0.97-1.41, *P* = .09), mirtazapine; 1.17 (1.00-1.38, *P* = .05), trazodone; 1.22 (1.04-1.45, *P* = .02), venlafaxine; and 1.29 (1.03-1.61, *P* = .03), milnacipran.
Conclusion: The short-term risk of T2D was significantly higher in the milnacipran and venlafaxine groups than in the fluoxetine group. All other ADs except milnacipran and venlafaxine showed no difference in the risk of developing T2D compared to fluoxetine. These results suggest that clinicians should be mindful of the risk of developing T2D when administering milnacipran and venlafaxine to patients.

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INTRODUCTION

The relationship between antidepressants (ADs) use and the risk of type 2 diabetes (T2D) is complex and incompletely understood. The relationship can vary depending on the specific type of AD and individual factors. Various classes of ADs, such as tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), etc., have different effects on metabolic parameters.[1,2] Overall, SSRIs, such as fluoxetine, sertraline, and escitalopram, are generally considered to have neutral or potentially positive effects on glucose metabolism.[3-5] Their use is less likely to cause weight gain than that of the other classes of ADs. In contrast, TCAs such as amitriptyline and imipramine are associated with weight gain and changes in glucose metabolism.[6,7] Moreover, TCA use may increase the risk of developing T2D, especially in individuals who are predisposed to metabolic disorders. Various ADs other than TCA also increase the risk of developing T2D.[8] A 3-arm randomized controlled trial (RCT) published in 2008 was the first to report a positive correlation between the use of ADs and new-onset T2D.[9] However, recent observational studies cast doubt on this association.[8,10-12] According to a meta-analysis, the risk of glycemia is increased by SSRI use.[13] Nevertheless, the effect of different AD types on the likelihood of developing T2D at onset is unclear. In contrast, fluoxetine has also been reported to benefit T2D patients with depression by regulating lipid profile and glycemic index.[3] A meta-analysis including 5 randomized placebo-controlled trials showed that short-term fluoxetine treatment could lower triglyceride and

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HbA1c levels in patients with T2D, as well as lead to weight loss.[3] Another factor to keep in mind regarding the relationship between AD use and T2D is the effect of antipsychotic drugs used in addition to ADs. For example, certain atypical antipsychotics, which are sometimes used as adjuncts to ADs, may cause an increased risk of T2D due to their impact on insulin sensitivity and weight gain.[14,15]

This study aimed to evaluate the relative risk of developing T2D in patients using various ADs, excluding TCAs. To this purpose, I selected fluoxetine, which has been reported to have a weight loss effect in some studies, as a control and compared it with other ADs to evaluate the risk ratio for developing T2D. To eliminate the influence of antipsychotics on the development of T2D, I extracted data only from patients who did not use any antipsychotics from those who used ADs and analyzed the risk of developing T2D. Further, I also investigated the short-term risk of T2D in depressed patients who used various ADs, including fluoxetine, compared with that in depressed patients depressed patients who did not use any ADs.

MATERIAL AND METHODS

Data Source

This study used an open database standardized from the Health Insurance Review and Assessment Service (HIRA) claims data in the Common Data Model (CDM) format (FNET_HIRA2017_OPEN [n=1,456,489]). The patient dataset used in this study corresponded to 3% of the total Korean population. A central database called the HIRA is used by the Korean government to manage the country's statutory national health insurance program. This database includes all prescription and treatment claim records for approximately 99% of the Korean population.[16] All HIRA data from 2012 to 2017 were mapped to standardized data from the Observational Medical Outcomes Partnership Common Data Model (OMOP CDM) schema developed by the Observational Health Data Sciences and Informatics (OHDSI) Network with standard vocabulary and ontology.[17] HIRA data are provided in segments on an annual basis; in this study, a 1-year follow-up study was conducted using the 2017 HIRA data. The Institutional Review Board (IRB) of Keimyung University Dongsan Hospital approved this study (IRB number: DSMC 2023-11-067), and the need for informed patient consent was waived.

MAIN POINTS

- Patients using milnacipran and venlafaxine were identified as having an increased short-term risk of T2D compared to those using fluoxetine.
- All other ADs except milnacipran and venlafaxine showed no difference in the risk of developing T2D compared to fluoxetine.
- When comparing the risk of developing T2D in depressed patients who used various ADs and those who did not use any ADs, the ADs that increased the risk of developing T2D in the short term were duloxetine, venlafaxine, milnacipran, mirtazapine, and trazodone.
- This study shows that even short-term use of some ADs within 1 year can increase the risk of developing T2D and shows that among atypical ADs excluding TCAs, serotonin and norepinephrine reuptake inhibitors (SNRIs) rather than selective serotonin reuptake inhibitors (SSRIs) increased the risk of developing T2D in the short term.

Study Design and Cohorts

The OMOP CDM was developed by Observational Health Data Sciences and Informatics (OHDSI), which established an international network of researchers and observational health databases with a central coordinating center housed at Columbia University. The OMOP CDM standardizes clinical coding systems and offers a uniform format for healthcare data, allowing analytical codes to be exchanged between network participants' datasets. This standardization makes it possible to combine and analyze data from different sources and institutions. Tables can be used in the CDM to store information on conditions (diagnoses), drugs, procedures, clinical observations, and patient demographics. The OMOP CDM uses standardized vocabulary to code medical ideas. The inclusion of concepts from sources like SNOMED CT (Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT)), Logical Observation Identifier Names and Codes (LOINC), and Medical Prescription Normalized (RxNorm) guarantees that medical terminology is consistently represented.[18] The diagnostic codes used for cohort extraction were defined according to SNOMED-CT.[19] These codes correspond to the terminology found in the 8th version of the Korean Classification of Diseases (KCD-8), which is essentially an update of the ICD-10.[20] The code for the drugs used in the cohort extraction process was RxNorm.

All patients registered in the HIRA database whose data were standardized using the OMOP CDM were included. Patients aged ≥10 years with no history of use of ADs and no history of T2D, regardless of whether they had a diagnosis of any depressive disorder, were eligible for this study. The SNOMED CT codes for diabetes mellitus used for the exclusion diagnosis and outcome measurement were 46635009 (type 1 diabetes), 44054006 (T2D), and 73211009 (diabetes mellitus). The RxNorm codes for drugs used in the cohort extraction process were: 4493, fluoxetine; 32937, paroxetine; 321988, escitalopram; 36437, sertraline; 42355, fluvoxamine; 10737, trazodone; 15996, mirtazapine; 72625, duloxetine; 39786 and 734064, venlafaxine (including desvenlafaxine), 588250 and 1433212, milnacipran (including levomilnacipran); 38253, tianeptine; 42347, bupropion; and 1455099, vortioxetine. Among these eligible patients, I only included in this study those who first used ADs between January 1 and December 30, 2017. In this study, I compared the incidence of T2D that occurred within 1 year after using AD in the experimental and control groups. To minimize the impact of antipsychotics on T2D development and keep the study

groups as clear as possible, I completely excluded patients who had used any antipsychotics from the analysis. Patients using fluoxetine were included in the control group, whereas patients using ADs other than fluoxetine were included in the experimental group. This study also assessed the short-term risk of T2D in patients using various ADs compared to patients with depression who did not use any ADs. In that case, the control group consisted of patients with depression who did not use any ADs, while the experimental group consisted of patients with depression who used various ADs, including fluoxetine. Patients with similar clinical characteristics to the experimental group were selected for the control group through 1:1 matching using propensity score matching (PSM).[21] Propensity score matching is a statistical technique used to make fair comparisons between experimental and control groups in observational studies. This method is employed to achieve balance between groups based on observed characteristics when random assignment is not feasible. I used 0.2 of the pooled SD of the logit of the propensity score as the caliper width for PSM. Age, sex, comorbidities, prior medications, and Romano's adaptation of the Charlson Comorbidity Index[22] were the covariates used for PSM. Supplementary Figures 1-12 present the flow sheets for data extraction in the 12 cohorts. Data extraction was performed using the Federated E-Health Big Data for Evidence Renovation Network (FeederNet) computer application, a Korean health data platform built on the OMOP-CDM.[23] Approximately fifty large general hospitals in Korea provide their electronic medical record (EMR) data, which FeederNet standardizes and de-identifies. All data are kept safe and secure, guaranteeing that no private information will be revealed. By granting researchers who are registered FeederNet members access to the FeederNet server (https://feedernet.com), this data platform has made it easier to conduct research across several institutions. As the preliminary analysis showed that T2D occurred in all cohorts 120 days after the index date, the primary outcome of this study was the occurrence of T2D at least 120 days after the index date. Type 2 diabetes was considered to have occurred when the illness persisted for at least 14 days.

Statistical Analysis

The statistical analysis was conducted using the open-source OHDSI CohortMethod R package, whereas the large-scale analytics were conducted using the Cyclops R program. The computer software used in this study was ATLAS version 2.7.5, and FeederNet was used for the analysis. ATLAS is an open-source program designed as a component of the OHDSI to offer a unified interface for patient-level data and analytics. The open-source ATLAS software package allows researchers to conduct scientific analysis using OMOP CDM-transformed standardized observational data. Differences between the clinical and demographic characteristics of the experimental and control groups before and after PSM are presented as percentages and standardized differences, respectively. To assess the balance between the experimental and control groups at baseline, ATLAS computed the standardized mean differences (SMDs) for each variable measured. The SMD is a measure of the distance between the means of 2 groups based on one or more variables. This is often used in practice to measure balance on individual covariates before and after PSM. It is not advised to display *P*-values from *t*-tests or chi-square tests when examining the covariate balance because the null hypothesis may not always be rejected, which does not imply that the covariates are well balanced between the 2 groups. Statistical tests generally judge statistical significance based on the *P*-value. Here, as the sample number decreases, the test power decreases, so the *P*-value increases. Since PSM excludes unpaired data, the sample size decreases and the *P*-value increases, so the result can be obtained that there is no significant difference in baseline characteristics between the 2 groups.[24] Therefore, in order to confirm the difference in baseline characteristics between the 2 groups after matching, a method that is not affected by the sample size must be used. It is advised to use standardized biases, sometimes referred to as SMDs, to evaluate how well the 2 groups' variables are balanced.[25] According to guidelines, acceptable standardized biases can be roughly defined as 0.1 or 0.25 of SMD; larger standardized biases suggest that groups are too different from one another to make comparisons with any degree of reliability.[26] For good variable balance, the absolute SMD should be less than 0.25.[26,27] Kaplan–Meier survival analysis was used to examine the variation in T2D-free state probabilities between the experimental and control groups. I used the log-rank test to compare the cumulative incidence between the 2 groups. A 2-sided *P*-value of less than .05 was considered to be statistically significant. The survival curves for the 2 groups were compared using the log-rank test. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the incidence of T2D associated with ADs were calculated using a multivariate Cox proportional hazards model.

RESULTS

Cohort Characteristics

The baseline characteristics of 12 cohorts before and after PSM are presented in Supplementary Tables 1-12. Following PSM, the baseline characteristics of patients in the experimental and control groups did not differ by more than 0.25 absolute SMD in any of the 12 cohorts, and all variables were well balanced.

Outcome Assessment

Table 1 presents the number of patients, duration of follow-up time (person-years), number of cases of

Table 1. Patient Cohort Sizes, Primary Endpoint Events, Incidence Rates, and Minimum Detectable Relative Risk for 12 Cohorts

Group	No. of Patients	Person-years	No. of T2D	IR	MDRR
Paroxwetine cohort					
Experimental	1871	872	327	374.78	
Control	1871	852	341	400.00	1.24
Escitalopram cohort					
Experimental	2091	977	293	299.72	
Control	2091	968	310	320.05	1.26
Sertraline cohort					
Experimental	1739	791	342	432.24	
Control	1739	786	324	411.95	1.24
Fluvoxamine cohort					
Experimental	336	143	86	599.87	
Control	336	147	78	527.89	1.55
Trazodone cohort					
Experimental	1901	868	353	406.54	
Control	1901	860	319	370.58	1.24
Mirtazapine cohort					
Experimental	1031	438	292	665.90	
Control	1031	454	253	557.11	1.27
Duloxetine cohort					
Experimental	1809	761	490	643.05	
Control	1809	806	416	515.91	1.20
Venlafaxine cohort					
Experimental	1414	616	353	572.27	
Control	1414	631	289	457.39	1.25
Milnacipran cohort					
Experimental	610	244	201	821.97	
Control	610	264	160	605.98	1.34
Tianeptine cohort					
Experimental	2113	987	300	303.94	
Control	2113	973	329	337.99	1.25
Bupropion cohort					
Experimental	917	425	156	366.44	
Control	917	405	170	419.17	1.36
Vortioxetine cohort					
Experimental	746	323	170	524.81	
Control	746	333	149	446.64	1.37

IR, incidence rate (per 1000 person-years); MDRR, minimum detectable relative risk; No., number; T2D, type 2 diabetes.

dementia (primary outcome), incidence rate (IR; per 1000 person-years), and minimum detectable relative risk after adjusting for the propensity scores in 12 cohorts. Figure 1 presents the observed HRs and 95% CIs for the incidence of T2D associated with ADs in the various AD groups compared with that in the fluoxetine group. The short-term risk (HR) of T2D was statistically significantly higher in depressive patients using milnacipran and venlafaxine that in depressive patients using fluoxetine. Further, I also investigated the short-term risk of T2D in depressive patients who used various ADs, including fluoxetine, compared with that in depressive patients who did not use any ADs. The results are presented in Figure 2. The short-term risk (HR) of T2D was statistically significantly higher in depressive patients using duloxetine, venlafaxine, milnacipran, mirtazapine, and trazodone than that in depressive patients who did not use any ADs.

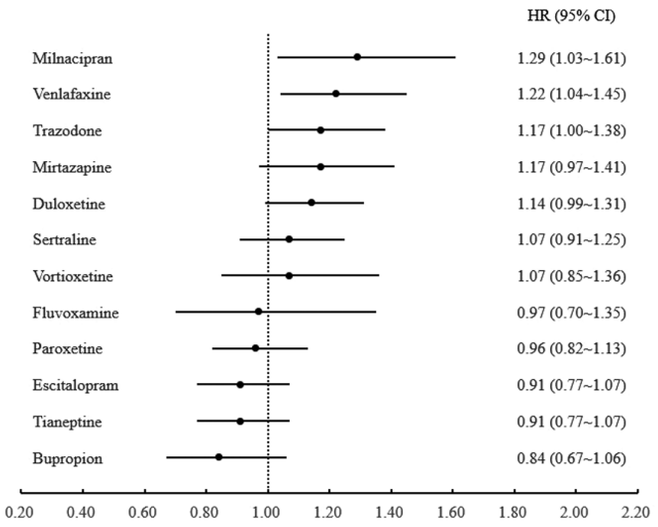

Figure 1. The observed hazard ratio and 95% confidence interval for the incidence of type 2 diabetes in the various antidepressant groups compared with that in the fluoxetine group. HR, hazard ratio; CI, confidence interval.

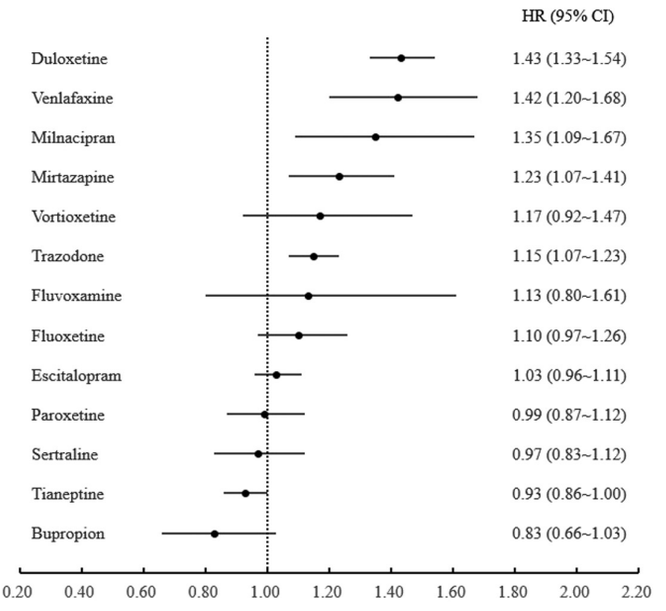

Figure 2. The observed hazard ratio and 95% confidence interval for the incidence of type 2 diabetes in **depressed patients** who used various antidepressants, including fluoxetine, were compared with those in **depressed patients** who did not use any antidepressants. HR, hazard ratio; CI, confidence interval.

Survival Curves

I visually assessed the proportionality assumption underpinning the Cox model using Kaplan-Meier survival curves. Supplementary Figures 13-24 show the Kaplan-Meier survival curves for T2D-free probability in the experimental and control groups of the 12 cohorts.

DISCUSSION

To assess the risk of developing AD-associated T2D, this study compared the short-term risk of T2D between patients using various ADs and patients using fluoxetine, which is associated with weight loss. Milnacipran and venlafaxine were associated with a higher risk of T2D than fluoxetine. All other ADs except milnacipran and venlafaxine showed no difference in the risk of developing T2D compared to fluoxetine. On comparing the risk of developing T2D in patients with depression who used various ADs with those who did not use any ADs, the ADs that increased the short-term risk of developing T2D were duloxetine, venlafaxine, milnacipran, mirtazapine, and trazodone.

Previous observational[28] and case-control studies[29] have suggested a link between long-term AD use and an increased risk of T2D. Nevertheless, this significant correlation was not supported by other several observational studies.[30-32] In contrast, other meta-analyses reported an association between AD use and T2D.[10,11,12] Most previous studies have investigated the relationship between AD use and T2D by types of AD. Few studies have investigated the relationship between individual AD use and the risk of developing T2D. Nguyen et al[33] conducted case/non-case studies using VigiBase®, the unique World Health Organization global database of reported potential adverse drug reactions (ADRs) of medical products, in which they identified signals of T2D associated with individual AD. ADs as a whole, 3 classes of ADs (TCAs, SSRIs, and "other" ADs), and 15 specific ADs in particular all showed significant T2D signals. The ADs that were most frequently associated with T2D were 3 SSRIs, namely escitalopram (adjusted reporting odds ratio 1.15 [1.07-1.25]), paroxetine (1.15 [1.07-1.23]), sertraline (1.23 [1.17-1.31]), and 3 "other" ADs, namely duloxetine (1.15 [1.07-1.23]), trazodone (1.20 [1.09-1.32]), and venlafaxine (1.15 [1.08-1.23]).[12] They also conducted linear regression analyses to investigate the relationship between the T2D signal ranked between ADs and their binding affinities for 9 targets (serotonin, norepinephrine, dopamine transporters, 5-HT2C serotonin, D2 dopamine, α1, α2 adrenergic, M3 muscarinic, and H1 histamine receptors). As a result, they found a significant correlation between serotonin transporter affinity and the T2D reporting signal with ADs in VigiBase®, but not for the 8 other targets: 2 transporters (norepinephrine and dopamine transporters) and 6 receptors (5-HT2C, D2, α1, α2, M3, H1).

In this study, I compared the risk of developing T2D in patients with depression who used various ADs with those who did not use any AD. Two types of ADs associated with the development of T2D were SNRIs (duloxetine, venlafaxine, and milnacipran) and "other" ADs (mirtazapine and trazodone); SSRIs were not associated with the development of T2D. In a relative comparison with fluoxetine, the ADs evaluated as having a higher risk of developing T2D than fluoxetine were duloxetine and mirtazapine. These results were different from those that

Nguyen et al. reported. [33] In a study by Nguyen et al,[33] 3 SSRIs (escitalopram, paroxetine, and sertraline) were also reported to be related to the occurrence of T2D, which may be related to the methodological differences in their study, which used a case/non-case method. A case/non-case analysis is a method for assessing drug safety by examining the disproportionality of ADR notifications in a pharmacovigilance database.[34,35] Disproportionality analysis identifies the distribution imbalance of a combination of a specific drug and a specific adverse event; it is a data mining technique mainly used to detect ADRs.[36] This study compared individual ADs with fluoxetine for investigating T2D occurrence, but Nguyen et al[33] compared individual ADs with all the other ADs found in VigiBase® for investigating a putative T2D signal. Therefore, the slightly different results of the above 2 studies could have been due to the different characteristics of the control groups used to compare the risk of developing T2D in individual ADs. In this study, there was no significant difference in the incidence of T2D when a specific SSRI was compared with fluoxetine, which is an AD of the same class. However, Nguyen et al[33] compared a certain SSRI to all other ADs, which included other SSRIs and other types of ADs. The low rate of T2D in other types of ADs may have led to a higher estimate of the risk of getting T2D for a certain SSRI. In fact, the observed odds ratio for T2D in Nguyen et al's study was 1.11 for SSRIs, 0.72 for TCAs, 0.62 for MAOIs, and 1.08 for "other" ADs.[33]

A nested case-control study reported that the long-term use of fluvoxamine, paroxetine, and venlafaxine increased the risk of diabetes.[29] This study found that the association between AD use and the development of diabetes was related to the duration of AD exposure and drug dosage. The risk of diabetes increased when ADs were used for more than 2 years at moderate-to-high doses, but no association with diabetes was observed when ADs were used at low doses or for less than 1 year.[29] As this study was a short-term follow-up study after AD use, the duration of AD use was less than 1 year. In contrast to Andersohn et al's study,[29] this study found that SNRIs (duloxetine, venlafaxine, and milnacipran) and "other" ADs (mirtazapine and trazodone) were associated with a high risk of developing T2D after short-term (<12 months) use. A recent study reported in Japan, a country of the same Asian race, also found that the AD-exposure group had a higher risk of T2D than the AD-nonexposure group, and these findings were identified in all groups, from the short-term low-dose group (HR 1.27; 95% CI 1.16-1.39) to the long-term high-dose group (HR 3.95; 95% CI 3.31-4.72) [36]. A Japanese study by Miidera et al[37] did not analyze the risk of T2D by AD type or individual AD, making direct comparisons with the results of this study challenging. There are also differences between the methodology of this study and that of the Japanese study by Miidera et al.[37] Differences in the study subjects' characteristics can explain the significant difference in T2D frequency between this study and Japanese study. This study used medical claims data from patients who received treatment at medical institutions, but the Japanese study used data that included both medical claims data and health check data from employees at health insurance associations and their families.[37] Therefore, the inclusion of many healthy individuals in the data may have understated the incidence of T2D in the Japanese study. However, the common finding of 2 studies, that the risk of developing T2D increases even with short-term use of some ADs, is meaningful. The increased incidence of T2D after short-term use of ADs seen in this study and the Japanese study may be related to racial differences. Therefore, further studies are needed to assess whether there are differences in vulnerability to AD-induced diabetes among ethnicities. Therefore, more research is required to determine if different ethnic groups are vulnerable to AD-induced diabetes.

This study has several strengths. First, to the best of our knowledge, this is the first study to investigate the risk of T2D for individual ADs, except for the studies by Nguyen et al[33] and Andersohn et al,[29] which were mentioned above. Second, this was a nationwide population-based study using a central database called the HIRA, which is used by the Korean government to manage the country's statutory national health insurance program. The strength of the HIRA dataset lies in its representativeness of the total patient population in Korea as well as its advantages in generalizing the population. Researchers can follow the same subjects over time because the database continuously accumulates records of each beneficiary's diagnosis and use of healthcare services. The longitudinal features of the data might be useful for cohort studies and for investigating long-term outcomes (effects) of exposure that might not be immediately noticeable. Moreover, only healthcare professionals supply data in the HIRA, allowing researchers to avoid inaccuracies caused by patient self-reporting and non-response, which is a common issue in survey-based research.

This study also has several limitations. First, this study used the CDM's de-identified database to protect patients' personal information; in contrast to medical record review data, it was impossible to confirm specific clinical information. Second, there may be disparities between diagnosis coding and patients' true medical conditions, as well as up-coding concerns, because of insurance reimbursement policies and the fee-for-service payment model.[38,39] This disparity raises the possibility of bias or, at the at least, compromises the validity of the study by suggesting that some patients may not actually have the medical conditions that correspond to their diagnosis. Third, the process of transforming electronic medical records into CDM databases may lead to issues with data quality, which can affect the CDM data used in this investigation. Lastly, because this study used the 2017

HIRA data provided as segmented data on a yearly basis, the T2D incidence rate due to long-term administration of ADs could not be investigated, and only the T2D incidence rate over a one-year period was investigated. Therefore, a long-term follow-up study using 5-year data combining segmented HIRA data from 2012 to 2017 with the same patient ID number is needed in the future.

In conclusion, when comparing the short-term risk of T2D in patients using fluoxetine with that in patients using various ADs, the drugs associated with a higher risk of developing T2D than fluoxetine were milnacipran and venlafaxine. Additionally, this study also examined the risk of T2D in patients with depression who used various ADs and in patients who did not use any AD. ADs with an increased risk of developing T2D in the ADs-used group compared to the ADs-non-used groups were duloxetine, venlafaxine, milnacipran, mirtazapine, and trazodone. This study shows that even short-term use of some ADs within 1 year can increase the risk of developing T2D and shows that among atypical ADs excluding TCAs, SNRIs rather than SSRIs increased the risk of developing T2D in the short term.

Availability of Data and Material: The datasets analyzed in this study are not publicly available because they were performed only through a mapping process of existing data sets on a computer network. However, further information is available from the corresponding author upon reasonable request.

Ethics Committee Approval: This study was approved by Ethics Committee of Keimyung University Dongsan Hospital (Approval No: DSMC 2023-11-067, Date: 5 Dec 2023).

Informed Consent: The requirement for obtaining informed consent from the patients was waived.

Peer-review: Externally peer-reviewed.

Declaration of Interests: The authors have no conflicts of interest to declare.

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