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ORIGINAL PAPER

The association between antidepressant use and deaths from road traffic accidents: a case-crossover study

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Abstract

Purpose Antidepressants are some of the most commonly used psychiatric medications, but little information is available about the effects of antidepressant treatment on the risk of traffic accidents across classes of antidepressants or associated with each substance individually. To investigate the relationship between exposure to antidepressants and risk of fatality in road traffic accidents.

Methods We used a Korean national road traffic authority database linked with a national health insurance database between January 1, 2010 and December 31, 2014 and applied a case-crossover design. The study subjects were drivers in South Korea who died from traffic accidents and who had prescriptions for antidepressants within 1 year prior to the date of the accident. We compared the status of prescription for antidepressants with the hazard period and four matched control periods using conditional logistic regression, adjusting for other drug use. The trends of antidepressant utilization were described in terms of the number of prescriptions. A case–case-time-control design was applied to drugs with an increasing trend in use and a significant case-crossover odds ratio (OR).

Results A total of 1250 antidepressant-using drivers were included, and an increased risk was observed during the 30-day hazard period (adjusted OR 1.30; 95% CI 1.03–1.63). Selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) showed significant risks, but tricyclic antidepressants did not. However, the associations of all antidepressants, SSRIs, SNRIs, escitalopram, and duloxetine did not remain significant after adjusting for trends in utilization. Paroxetine and milnacipran were associated with increased risks, with no obvious increase in their utilization, but the possibility of confounding by indication could have affected the results for milnacipran.

Conclusion Considering the trends of antidepressant prescription and utilization, the use of paroxetine increased the risk of fatal traffic accidents.

Keywords Antidepressants · Traffic accidents · Case-crossover design · Pharmacoepidemiology

Introduction

Depression, one of the most common mental illnesses, is highly prevalent throughout the world [1]. Depressive disorders greatly impair social and occupational functioning and cause a considerable social burden. According to a study of the global burden of disease, depression is the fourth leading cause of early death and disability in the world, and is predicted to become the second leading cause by 2020 [2–4]. For many years, antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) have been recommended as the treatment of choice for depression [5]. However, the possibility of antidepressant-related adverse events, including

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impaired psychomotor and cognitive function, also has been frequently noted [6, 7]. Because the impairment of cognitive and psychomotor functions such as reaction time could directly affect the ability to drive an automobile, questions have been raised regarding whether the use of antidepressants increases the risk of traffic accidents [8].

Several epidemiologic studies have documented potential associations between antidepressant use and the risk of road traffic accidents, mainly focusing on tricyclic antidepressants (TCAs) and SSRIs. Previous studies showed TCAs to be associated with the risk of road traffic accidents [9–11], and other studies reported such an association for SSRIs [11–13]. However, Barbone et al., reported that neither TCAs nor SSRIs were significantly associated with road traffic accidents [14], and according to Ravera et al., the association was only significant for SSRIs, and not for other antidepressants [15]. In contrast to TCAs and SSRIs, the associations of road traffic accidents and exposure to SNRIs have rarely been investigated, and few studies have reported results for specific antidepressants, besides a study reporting a significant risk associated with high doses of amitriptyline [9]. Moreover, previous studies need to be interpreted in light of the following limitations: the study participants were limited to patients with a specific disease [11] or the elderly [9–11, 16], or possible confounding variables, such as alcohol consumption [10, 12, 16], were not considered. A population-based case-crossover study using a database constructed by linking a traffic accident database and a health insurance claim database that includes information on age, sex, comorbidities, and antidepressants could be a way to resolve the limitations described above. As the case-crossover design compares the exposure of the case period to that of the control period within the same individual, the problem of comparability between case and control that occurs in case-control studies would be overcome, and confounding by unmeasurable factors could be controlled [17].

Therefore, the aim of this study was to assess the association between antidepressant use and death from road traffic accidents in the Korean population using a large representative database, considering trends in antidepressant use.

Methods

Data source

We linked the Korean Traffic Accident Analysis System (TAAS) data provided by the Road Traffic Authority with data from the National Health Insurance Service (NHIS) database for identifying the diagnoses of patients who died from a traffic accident and the drugs prescribed to them during a period before the accident between January 1, 2010 and December 31, 2014. The TAAS data (http://taas.koroad.or.kr/) contain variables on the accident characteristics (date, time, location, and type of accident), vehicles, drivers, situations (weather, type of road, road condition, velocity, speed limit, and whether drunk driving was involved), and causes of the accidents (personal factors, vehicle factors, and road environmental factors). A fatal accident was defined as a case in which death occurred within 30 days after the accident.

The NHIS was launched in 1977 and has achieved universal coverage of the entire population of South Korea since 1989. The claims database includes comprehensive information on patient demographics, diagnoses, procedures, and prescriptions [18]. All Koreans have a unique identification number (the resident registration number, RRN), and the subjects included in both the NHIS and TAAS data are indexed by RRN. Permission for database access and linkage was obtained from both institutions only for records of the deceased, whose information is not covered by the Korean Act on the Protection of Personal Information. The extracted RRNs from the TAAS data were matched to the NHIS database, and the de-identified database was provided by NHIS. The full protocol for data linkage and construction of the study dataset has been published elsewhere [19].

The present study has been exempted from review by the Institutional Review Board of Seoul National University Hospital (IRB number: E-1507-089-689).

Study design

We conducted a case-crossover study to estimate the risk of death from a traffic accident associated with antidepressant use. The case-crossover design was introduced in 1991 to evaluate the short-term effect of exposure on an acute event [20]. We deemed our study to be suitable for a case-crossover design, as our outcome of interest, fatality due to a traffic accident, is a definite acute event, and the occurrence of this event might be influenced by the transient effect of our exposure of interest, the antidepressant. As a case-only design, each case is matched with itself as a control and time-invariant confounders can be controlled by design. We defined the period before the accident as the hazard period, which is the time interval during which a population experiences an increased risk of the outcome caused by the trigger, and we defined the preceding four periods as control periods [21].

The length of the hazard and control periods was selected to be 30 days, according to previously conducted studies that related antidepressant use to traffic accidents [13, 22]. Between the hazard period and control period, a washout period was allocated to minimize the carryover effects of exposure during control periods. As 99.9% of antidepressant prescriptions were for a duration of less than 180 days, we chose 180 days as the washout

period, and a sensitivity analysis for 60-day, 90-day, 120-day, 150-day, 180-day washout periods was conducted (Fig. 1). The same time periods were applied to identify the exposure to antidepressants and comedications.

Subjects and exposure to antidepressants

We defined the inclusion criteria for study participants as the following: (1) drivers who died in road traffic accidents between January 1, 2010 and December 31, 2014, (2) patients who matched with the RRNs in the NHIS database, (3) patients who visited a medical institution within 1 year before the accident, and (4) patients who were prescribed an antidepressant at least once. Patients who were identified as drunk while driving, which was defined as a 0.05% blood alcohol concentration and above, were excluded.

The antidepressants included TCAs, SSRIs, SNRIs, and others. We identified the possession of an antidepressant during each period using the prescription date and duration and considered it as the exposure to an antidepressant. The impact of changes in the use of all antidepressants and each class of antidepressants on fatal road traffic accidents was assessed. Changes in antidepressant use comprised initiation and discontinuation. Initiation of antidepressants was defined as occurring when a patient was prescribed an antidepressant with no prior use in the previous 4 months [23], and discontinuation was considered to have occurred when 4 months had passed without a new prescription of an antidepressant after the end date of the last prescription.

In a case-crossover study, the results must be interpreted according to the trend of exposure. We identified the annual drug utilization measured by the number of prescriptions using the national patient sample from the Korea Health Insurance Review and Assessment Service database (HIRA-NPS). The annual utilization of total antidepressants, TCAs, SSRIs, SNRIs, and other antidepressants was described for the period between 2010 and 2014.

Statistical analysis

Patient characteristics, including age, gender, and comorbidities, were quantified as proportions and means with standard deviation. Conditions related to the likelihood of an accident were included as comorbidities based on previously published guidelines, and included diabetes mellitus, hypoglycemia, psychosis, depression, Parkinson disease, dementia, seizures, sleep disorders, macular degeneration, diabetic retinopathy, glaucoma, vestibular disorders, myocardial infarction, stroke, hypotension, chronic obstructive pulmonary disease, asthma, dizziness, fatigue, syncope, and arthritis.

The proportions of characteristics concurrent with the fatal accident were calculated. The month of the accident, time of the accident, whether it was day or night, the weather, road conditions, the type of accident, and the responsibility score were included. Day and night were classified using sunrise and sunset times from the data of the Korea Meteorological Administration, compared with the time of the accident. We calculated the responsibility score to assess the driver's culpability in an accident by adapting the methodology suggested by Robertson and Drummer [24]. We considered the following factors: the road condition, condition of the vehicle, driving conditions, type of accident, obedience to road laws, and difficulty of the task. Drivers with responsibility scores < 12 were classified as being culpable for the accident, and those with scores ≥ 12 were defined as non-culpable. The number of pairs with exposure in the hazard period and non-exposure in the control period, and the number of pairs with non-exposure in the hazard period and exposure in the control period were determined to calculate the Mantel–Haenszel estimates of the odds ratios (ORs) [22]. The adjusted (aORs) and 95% CIs were estimated by conditional logistic regression, and adjusted for the use of narcotics, muscle relaxants, antipsychotics, antihistamines, antispasmodics, antiemetics, hypnotics, change (initiation or discontinuation) in the use of antidepressants, and new onset of psychiatric conditions such as anxiety and psychosis/schizophrenia, which were considered to be potential confounders.

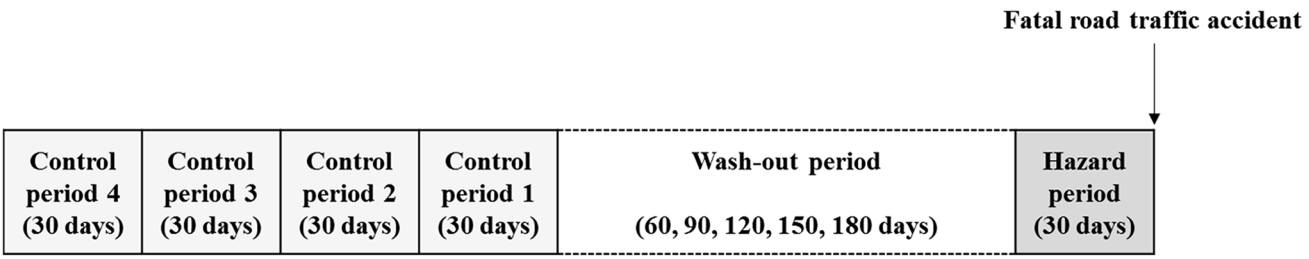

Fig. 1 Definition of hazard and control periods in this case-crossover study. The hazard period was defined as the 30 days before the index date. The wash-out period was defined as 60, 90, 120, 150, and 180 days

If the association of an exposure with fatal traffic accidents was significant, and an increasing trend in use was observed, a case–case–time-control design was applied to take those trends into account [25]. We matched the cases to controls derived from future cases by age (difference < 5 years), sex, and a permissible lag time between the case and control, in which the event date of a current case was between 30 and 210 days prior to the event date of a future case using a greedy algorithm.

All statistical analyses were performed with SAS software (version 9.4; SAS, Institute, Inc., Cary, North Carolina, USA).

Results

We identified 8880 drivers who died after road traffic accidents from January 1, 2010 to December 31, 2014. A total of 1464 drivers had at least one prescription for an antidepressant prior to the accident. Ultimately, 1250 antidepressant-using drivers were included (1114 men and 134 women) after excluding people who were indicated to have been driving while intoxicated in the TAAS data (Fig. 2). Forty-six percent of them were aged over 65 years and the mean age on the day of the accident was 59.7 ± 16.0 years (Table 1). Within the study population, 685 cases (54.8%) had a record of diagnosis of depression (International Classification of Diseases 10: F32–33). When classified by CCI score, the number of cases with a CCI score of ≤ 5 was slightly larger than that of cases with a CCI score > 5. The distribution of characteristics according to the history of comorbidities is presented in Table 1.

Fatal accidents occurred slightly more frequently in the summer (29.0%) and fall (27.6%) than in the winter (21.4%) and spring (22.0%). Most occurred during the daytime, with dry road conditions. Approximately half of the accidents involved a single vehicle, while the other half involved another vehicle (Table 1).

Among the study subjects ($n = 1250$), more than half were prescribed one class of antidepressants (69.7%) and 20.2% were prescribed two classes of antidepressants. In patients using only one class of antidepressants, a TCA was the most commonly prescribed antidepressant, followed by others, SSRIs, and SNRIs (Table 2).

The case-crossover analysis showed an increased risk of a fatal traffic accident with exposure to all antidepressants in the most recent 30 days, adjusting for the use of narcotics, muscle relaxants, antipsychotics, antihistamines, antispasmodics, antiemetics, hypnotics, change (initiation or discontinuation) in the use of antidepressants, and new onset of psychiatric conditions such as anxiety and psychosis/schizophrenia. In the analysis by the class of antidepressant, associations were found between antidepressant use and death from a traffic accident for those using an SSRI or

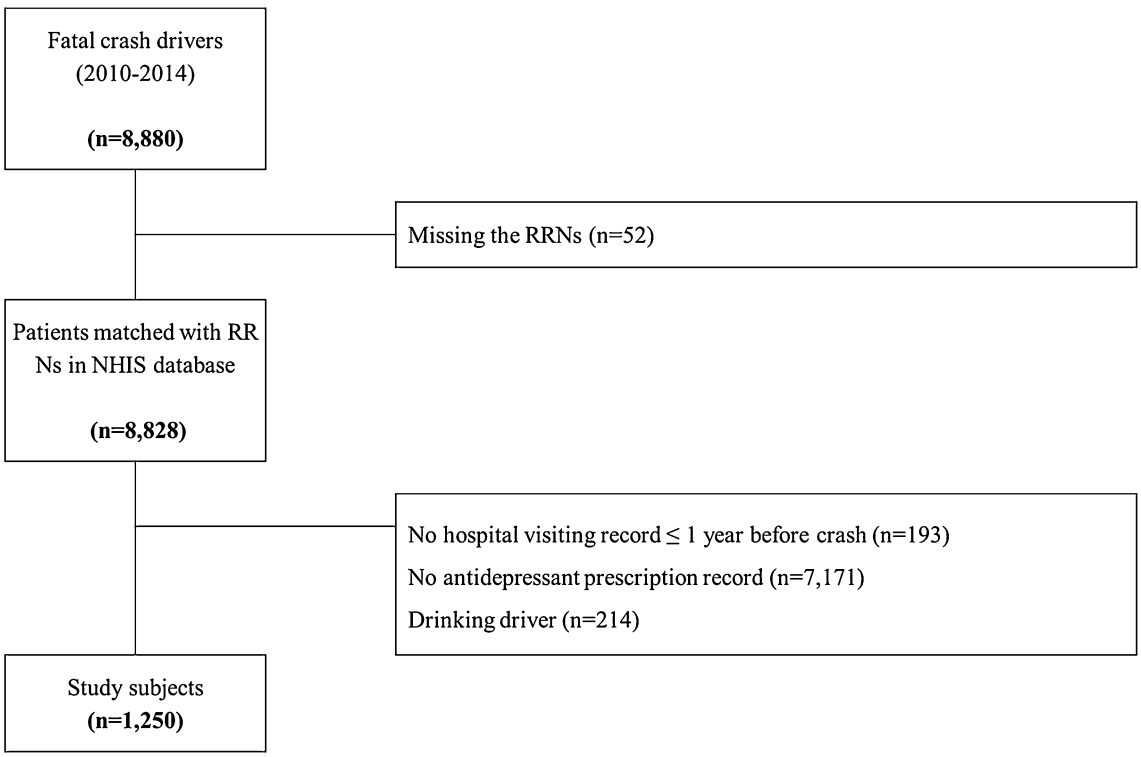

Fig. 2 Flowchart for the selection of study subjects. *RRN* resident registration number

Table 1 Characteristics of study subjects and fatal road traffic accidents

Driver's characteristics	*N* (total = 1,250)	%	Accident characteristics	*N* (total = 1250)	%
Gender			Month of the crash		
Male	1,114	89.1	Winter (Dec–Feb)	267	21.4
Female	134	10.7	Spring (Mar–May)	275	22.0
Unknown	2	0.2	Summer (Jun–Aug)	362	29.0
Age (mean ± SD)	59.7 ± 16.0		Fall (Sep–Nov)	346	27.6
< 65	675	54.0	Time of the crash		
≥ 65	575	46.0	00:00–05:00	169	13.5
History of comorbidity			06:00–11:00	381	30.5
Diabetes mellitus	605	48.4	12:00–17:00	450	36.0
Hypoglycemia	33	2.6	18:00–23:00	250	20.0
Psychosis	54	4.3	Day or night[a]		
Depression	685	54.8	Day	914	73.1
Parkinson disease	54	4.3	Night	336	26.9
Dementia	154	12.3	Weather		
Seizures	188	15.0	Clear	1031	82.5
Sleep disorders	435	34.8	Cloudy	77	6.2
Macular degeneration	41	3.3	Foggy	8	0.6
Diabetic retinopathy	97	7.8	Rainy	102	8.2
Glaucoma	262	21.0	Unspecified	116	9.3
Vestibular disorders	343	27.4	Road condition		
Myocardial infarction	351	28.1	Dry	1050	84.0
Stroke	228	18.2	Wet	155	12.4
Hypertension	54	4.3	Ice	19	1.5
COPD	224	17.9	Snowfall	9	0.72
Asthma	443	35.4	Others	17	1.36
Dizziness	422	33.8	Type of the crash		
Fatigue	63	5.0	Single vehicle	612	49.0
Syncope	34	2.7	Vehicle to vehicle	634	51.0
Arthritis	738	59.0	Others	4	< 0.1
Charlson's Comorbidity Index (CCI)			Responsibility score (RS)		
CCI ≤ 5	674	53.9	RS < 12 (culpable)	304	24.9
CCI > 5	576	46.1	RS ≥ 12 (non-culpable)	946	75.1

SD standard deviation, *COPD* chronic obstructive pulmonary disease

[a]Day/night was classified using mean sunrise/sunset time of the month from data of Korea Meteorological Administration

an SNRI, but not for those prescribed a TCA or another type of antidepressants. Among SSRI users, the highest risk was found for paroxetine users. Among SNRI users, the highest risk was found in those prescribed milnacipran, followed by those who used duloxetine. Neither changes in the use of all antidepressants nor changes in the use of each class were associated with an increased risk of death from a traffic accident (Table 3). In the sensitivity analysis for 60-, 90-, 120-, and 150-day washout periods, the risks were similar (Supplementary Table S1).

The annual utilization trends of antidepressants measured between 2010 and 2014 are presented in Figs. S1, S2, and S3. Except for TCAs, the other antidepressants, including SSRIs and SNRIs, showed slightly increasing trends in the number of prescriptions. The increasing trend of SSRIs could be explained by increases in prescriptions for escitalopram and sertraline, as no obvious increase in the utilization of fluoxetine and paroxetine was observed. Over this 5-year period, the prescribed volume of duloxetine increased sharply, while the prescribed volumes of milnacipran and venlafaxine stayed about the same.

The associations of fatal crashes with the use of all antidepressants, SSRIs, SNRIs, escitalopram, and duloxetine were not statistically significant after adjusting for time trends using a case–case–time-control design (Table 4).

Table 2 Antidepressant use in study subjects

Antidepressants	Number of subjects ($n=1250$)	%
Patients who prescribed one class of AD	871	69.7
TCA	442	35.4
SSRI	123	9.8
SNRI	22	1.8
Others[a]	284	22.7
Patients who prescribed two classes AD	252	20.2
TCA + SSRI	48	3.8
TCA + SNRI	13	1.0
TCA + others[a]	98	7.8
SSRI + SNRI	6	0.5
SSRI + others[a]	81	6.5
SNRI + others[a]	6	0.5
Patients who prescribed three classes of AD	100	8.0
Patients who prescribed four classes of AD	27	2.2

AD antidepressant, *TCA* tricyclic antidepressant, *SSRI* selective serotonin reuptake inhibitor, *SNRI* serotonin–norepinephrine reuptake inhibitor

[a]Others included monoamine oxidase inhibitors (moclobemide), bupropion, hyperici herba, mirtazapine, tianeptine, trazodone and amoxapine

Discussion

This was a nationwide population-based case-crossover study conducted to investigate the association between antidepressant use and the risk of a fatal road traffic accident. Our study showed that exposure to the use of any antidepressant within the 30 days prior to the accident was associated with a 30% increased risk of a fatal accident after adjustment for other drug use in the case-crossover design; however, the association was not significant in the case–case–time-control study design. The use of milnacipran or paroxetine showed statistically significant associations with experiencing a fatal accident, without an increasing trend in use.

The association of fatal traffic accidents with the use of all antidepressants was significant in the case-crossover design, whereas the ORs decreased toward null in the case–case–time-control design. The previous case-only design study showed a 1.07-fold increase in the risk of a traffic accident associated with antidepressant use [13]. The previous case–control study reported a 1.34-fold increase in the risk of a traffic accident, however, the risk was not significant when a case-crossover design was applied [26]. Considering that the washout period of the previous study was 30 days, whereas that of our study was 180 days, the trends in antidepressant use may have affected the results of the previous study to a lesser extent.

We found that changes in the use of antidepressants were more frequent in the hazard periods; however, the association was not statistically significant for the use of all antidepressants or each class of antidepressant. According to a case-crossover study using French national databases, the risk of traffic crashes increased after the initiation of antidepressant use (OR 1.49, 95% CI 1.24–1.79), and changes in antidepressant use (OR 1.32, 95% CI 1.09–1.60) [35]. Although the crude OR in our findings was similar to the crude OR of the previous study, the estimate of risk changed to 1.0 after adjusting for time-variant variables.

In the result of the case-crossover design in present study, the use of SSRIs or SNRIs in the most recent 30 days before the accident was associated with a significantly higher risk of a fatal accident, while the use of TCAs was not associated with a fatal accident, and these results were concordant with those of previous case–control studies [15, 26, 27]. However, the associations in SSRIs and SNRIs found in the case-crossover design were not significant after adjustment for trends in utilization, and these results were in agreement with the results of previous case-crossover studies [16, 26]. Contrary to our results from the case–case–time-control design, an association between undergoing antidepressant treatment with SSRIs and SNRIs and impaired driving was reported in a study conducted on patients with depression [28]. According to Ravera et al., it might be the case that the risk of suicide associated with SSRIs was related to the increased risk of a fatal accident as a possible explanation on the increased risk associated with SSRIs [15]. In a self-controlled case series study, an increased risk for completed suicide on the day of a SSRI prescription was observed [29], and in a case-crossover study, the risk for suicide during the 28 days following the initiation of an SSRI significantly increased [23]. Compared to SSRIs, few epidemiologic studies have been conducted focusing on SNRIs and the risk of traffic accidents. Campaign reported that venlafaxine withdrawal symptoms that might indicate noradrenaline-mediated syndrome, such as confusion, impaired coordination, and sensory disturbances, may occur within hours of cessation or reduction of the dosage, and as a result, noticeably affect an individual's ability to drive a car [30]. As venlafaxine was more frequently used in the hazard periods than in the control periods, the association was not significant after adjustment in our study.

Contrary to expectations based on the mechanism of TCAs and experimental studies, the use of TCAs has not been shown to have an association with fatal traffic accidents in recent epidemiologic studies [13, 26]. It is possible that this effect might be mediated by contraindications of TCAs. The sedating and anticholinergic effects of TCAs are well known, and some TCAs were included in the Beers criteria and French consensus panel list, which are explicit criteria designating potentially inappropriate medications for older people [31, 32]. Furthermore, TCAs are not considered to be first-line antidepressants and could have been used at lower

Table 3 Risk of fatal road traffic accidents associated with the use of antidepressant according to class of antidepressants

Medications	H0C1 ($n=5000$)		H1C0 ($n=5000$)		Crude OR (95% CI)	Adjusted OR(95% CI)
	n	%	*n*	%		
Total AD	429	8.6	596	11.9	1.56 (1.25–1.95)	1.32 (1.03–1.70)[c]
TCA	216	4.3	256	5.1	1.26 (0.91–1.75)	1.06 (0.74–1.52)[d]
SSRI[a]	159	3.2	248	5.0	1.93 (1.33–2.79)	2.04 (1.35–3.09)[d]
Escitalopram	87	1.7	136	2.7	1.85 (1.14–3.00)	1.68 (1.02–2.76)[e]
Fluoxetine	40	0.8	45	0.9	1.18 (0.54–2.61)	1.15 (0.52–2.55)[e]
Paroxetine	28	0.6	78	1.6	5.07 (2.27–11.33)	4.80 (2.05–11.22)[e]
Sertraline	23	0.5	22	0.4	0.94 (0.32–2.77)	0.61 (0.20–1.84)[e]
SNRI	25	0.5	97	1.9	6.63 (3.18–13.8)	9.85 (4.17–23.26)[d]
Duloxetine	17	0.3	63	1.3	5.93 (2.47–14.21)	6.08 (2.41–15.35)[f]
Milnacipran	1	0.0	20	0.4	19.98 (2.34–170.83)	27.01 (2.99–243.83)[f]
Venlafaxine	11	0.2	22	0.4	3.15 (0.78–12.69)	2.62 (0.65–10.54)[f]
Others[b]	212	4.2	259	5.2	1.32 (0.95–1.83)	0.96 (0.66–1.38)[d]
Change in use of						
Total AD	296	5.9	327	6.5	1.21 (0.95–1.55)	0.97 (0.74–1.28)[g]
Class of AD						
TCA	145	2.9	161	3.2	1.11 (0.78–1.56)	0.88 (0.61–1.26)[h]
SSRI	77	1.5	89	1.8	1.15 (0.72–1.83)	0.93 (0.57–1.51)[h]
SNRI	19	0.4	22	0.4	1.15 (0.45–2.93)	0.88 (0.33–2.37)[h]
Others[b]	130	2.6	171	3.4	1.31 (0.93–1.85)	1.09 (0.76–1.56)[h]

AD antidepressant, *TCA* tricyclic antidepressant, *SSRI* selective serotonin reuptake inhibitor, *SNRI* serotonin–norepinephrine reuptake inhibitor, *H0C1* number of pairs with non-exposure in the case period and exposure in the control period, *H1C0* number of pairs with exposure in the case period and non-exposure in the control period, *OR* odds ratio, *CI* confidence interval

[a]Citalopram and fluovoxamine could not be estimated due to small sample sizes

[b]Others included monoamine oxidase inhibitors (moclobemide), bupropion, hyperici herba, mirtazapine, tianeptine, trazodone and amoxapine

[c]Adjusted for the use of narcotics, muscle relaxants, antipsychotics, antihistamines, antispasmodics, antiemetics, hypnotics, change in use of all antidepressants, and new onset of psychiatric conditions such as anxiety and psychosis/schizophrenia

[d]Adjusted for the use of narcotics, muscle relaxants, antipsychotics, antihistamines, antispasmodics, antiemetics, hypnotics, change in each class of antidepressant (TCA, SSRI, SNRI, others) and new onset of psychiatric conditions such as anxiety and psychosis/schizophrenia

[e]Adjusted for the use of another class of antidepressant (TCA, SNRI, others), use of individual SSRIs, narcotics, muscle relaxants, antipsychotics, antihistamines, antispasmodics, antiemetics, hypnotics, change in the use of other class of antidepressants (TCA, SNRI, others), and new onset of psychiatric conditions such as anxiety and psychosis/schizophrenia

[f]Adjusted for the use of other class of antidepressant (TCA, SSRI, others), use of individual SNRIs, narcotics, muscle relaxants, antipsychotics, antihistamines, antispasmodics, antiemetics, hypnotics, change in the use of another class of antidepressant (TCA, SSRI, others), and new onset of psychiatric conditions such as anxiety and psychosis/schizophrenia

[g]Adjusted OR from model marked with superscript 'c'

[h]Adjusted ORs from model marked with superscript 'd'

doses for other psychiatric disorders besides depression and chronic pain [33].

Even if a statistically significant OR was observed, the possibility of the outcome being due to the trend of increasing use could not be ruled out, since antidepressant use showed an increasing trend during the study period. However, this possibility has been infrequently considered in previous studies, except the study of Rapoport et al., who conducted a sensitivity analysis to control for temporal trends [11]. Although we could not apply the case–time-control design, which uses exposure history data from a traditional control group, to estimate and adjust for the bias from temporal changes in prescribing [17], because it was not possible to link data of living drivers for use as a control group due to the Personal Information Protection Act, a case–case–time-control design was applied

Table 4 Case–case–time-control analysis for the risk of fatal road traffic accidents by the use of all antidepressants, SSRIs, SNRIs, escitalopram, and duloxetine

	CCO: adjusted OR (95% CI)	CCTC: adjusted OR (95% CI)
Total AD[a]	1.32 (1.03, 1.70)	1.05 (0.86, 1.28)
SSRI[b]	2.04 (1.35, 3.09)	1.04 (0.72, 1.50)
Escitalopram[c]	1.68 (1.02, 2.76)	1.06 (0.62, 1.81)
SNRI[b]	9.85 (4.17, 23.26)	1.23 (0.51, 2.95)
Duloxetine[d]	6.08 (2.41, 15.35)	0.57 (0.18, 1.86)

AD antidepressant, *OR* odds ratio, *CI* confidence interval, *CCO* case-crossover, *CCTC* case–case–time-control, *SSRI* selective serotonin reuptake inhibitor, *SNRI* serotonin–norepinephrine reuptake inhibitor

[a]Adjusted for the use of narcotics, muscle relaxants, antipsychotics, antihistamines, antispasmodics, antiemetics, hypnotics, change in use of all antidepressants, and new onset of psychiatric conditions such as anxiety and psychosis/schizophrenia

[b]Adjusted for the use of narcotics, muscle relaxants, antipsychotics, antihistamines, antispasmodics, antiemetics, hypnotics, change in each class of antidepressant (TCA, SSRI, SNRI, others) and new onset of psychiatric conditions such as anxiety and psychosis/schizophrenia

[c]Adjusted for the use of another class of antidepressant (TCA, SNRI, others), use of individual SSRIs, narcotics, muscle relaxants, antipsychotics, antihistamines, antispasmodics, antiemetics, hypnotics, change in the use of another class of antidepressants (TCA, SNRI, others), and new onset of psychiatric conditions such as anxiety and psychosis/schizophrenia

[d]Adjusted for the use of another class of antidepressant (TCA, SSRI, others), use of individual SNRIs, narcotics, muscle relaxants, antipsychotics, antihistamines, antispasmodics, antiemetics, hypnotics, change in the use of other class of antidepressant (TCA, SSRI, others), and new onset of psychiatric conditions such as anxiety and psychosis/schizophrenia

for exposures that were associated with fatal crashes and showed increasing trends. As a result, the increased risk of all antidepressants, SSRIs, SNRIs, escitalopram, and duloxetine observed in the case-crossover design did not remain in the case–case–time-control design. Therefore, only the increased risk associated with antidepressants with no trend of increasing use was interpreted as significant. Through this approach, significantly increased risks were found for paroxetine (an SSRI) and milnacipran (an SNRI).

Paroxetine, which showed the highest risk among SSRIs, additionally inhibits dopamine reuptake, and can impair the vigilance of drivers [34]. However, the impairment of vigilance by paroxetine at a dose of 20 mg in an experimental study did not result in impaired car driving performance, including brake reaction time, critical flicker fusion, and recognition reaction time [35]. In a double-blinded, 3-way crossover trial to assess the acute effects of paroxetine on driving performance compared to amitriptyline or placebo, paroxetine impaired neither driving performance nor cognitive function [36]. These experimental results seem consistent with the previous knowledge that SSRIs are not deleterious to car-driving patients. As a possible mechanism through which paroxetine increased the risk of fatal accidents, however, withdrawal syndrome is known to cause impairment in functions related to driving performance, although we could not measure it directly. Hindmarch et al. performed an experimental study to compare the effects of abrupt and brief discontinuation of fluoxetine, sertraline, paroxetine, or citalopram on cognitive function and psychomotor performance, and reported that only paroxetine-treated patients experienced significantly more cognitive failures, poorer quality of sleep, and an increase in depressive symptoms compared to some or all of the other drugs, suggesting these phenomena are not associated with SSRIs as a class [37]. Thus, paroxetine users may be at higher risk for an accident, even if they have the same level of compliance as other SSRI patients. In the real-world setting, unlike experimental studies where the administration of medication is strictly controlled, it is reasonable to consider withdrawal syndrome as a cause of fatal accidents.

Our results showed a nearly 27-fold increase in the risk of a fatal traffic accident associated with the use of milnacipran. This high risk is inconsistent with previous studies of the effects of milnacipran on driving safety. Hindmarch et al. found that milnacipran administered to volunteers did not affect driving performance in young people and improved the critical flicker fusion score in the elderly [38]. Studies of the effects of milnacipran on memory, cognition, and driving performance by Poirier et al. and Richet et al. confirmed that milnacipran did not affect the psychomotor function required for driving [39, 40]. Despite this safety information from clinical studies, 1 case of a traffic accident was reported in a re-examination study as a severe adverse event, which led to a change in the label of milnacipran in the Korean market, underscoring the importance of investigating associations between milnacipran and traffic accidents [41]. We confirmed that in the five fatal accidents included in the analysis in which the driver used milnacipran, a sleep disturbance was diagnosed 1 month–1.5 months prior to the accident, and we suspect that this comorbidity may have caused the traffic accidents. Another important fact is that milnacipran was recommended as a second-line drug among SNRIs for depressive disorders in the Korean Medication Algorithm Project for Depressive Disorder 2012 by the Korean Society for Affective Disorders and the Korean College of Neuropsychopharmacology [42]. Therefore, the population size of patients who were exposed to milnacipran in our study was very small, and the drug was usually used later in the clinical course, which might explain the exaggerated risk ratio observed in our study. Further studies are needed to confirm drug-specific associations.

One strength of this study was its high generalizability, since we used a national health insurance and traffic

accident database, which covered nearly the entire population of South Korea. As comprehensive information on drug use and traffic accidents was included in these databases, and the study drugs were all prescription drugs, the risk of recall bias was minimized. Using a case-crossover design, we were able to eliminate the bias due to time-invariant variables such as genetic factors, lifestyle, and the presence of a chronic disease.

However, our study also had several potential limitations. The NHIS database that was used for our study does not include information regarding whether prescription drugs were dispensed or not, which would improve the assessment of exposure to the drug. In addition, the fact that medications were prescribed does not imply that the patient actually took these medications according to the prescription. Even though we could not examine actual drug use, we measured adherence as a proxy, and the average medication possession ratio (MPR) of antidepressants for 1 year in the study population was 0.71 (SD 1.03), while the proportion of individuals with an MPR ≥ 0.8 was 30.8%. Although between-person confounding factors such as severity of depression and driving patterns, which is information usually lacking in claims databases, were controlled for by the study design, unmeasured time-variant confounding factors could not be controlled. Given the possibility that some individuals did not drive during the control periods, the results could have underestimated the risks of driving associated with the use of antidepressants. Additionally, the question of whether the association showed in our results was due to the antidepressants themselves or to symptoms of depression could be raised. Although it was not possible to control directly for the severity of disease or the exacerbation of symptoms, several approaches were considered in our study. A sensitivity analysis was conducted using various washout periods under the assumption that the closer the interval between case period and the control period, the more similar the symptoms would be, following the approach used in a previous case-crossover study [16]. The adjusted OR was consistent across the washout periods from 60 to 180 days. When adjusting for the use of antipsychotics and hypnotics, which may have been associated with psychiatric symptoms, the associations remained significant [43]. Furthermore, the outcome of the present study only included fatal accidents due to legal restrictions on the use of personal data, and the study results must be interpreted with a focus on fatal road traffic accidents. Fatal accidents could directly reflect the severity of the accident; however, the condition of the vehicle(s), the driver's medical condition, first aid, transfer to a medical institution, and the quality of treatment in the hospital also had an influence on the fatality of the accident. Further research is needed to examine the risk posed by exposure to antidepressants, including both fatal and non-fatal traffic accidents. While our study did not include all the other indications for the studied drugs in the analysis, fibromyalgia, which can be treated by milnacipran, was analyzed, since this condition may increase the risk of traffic accidents. Furthermore, an association of increased risk with milnacipran use was observed in our results. However, only one patient with fibromyalgia was included among the study subjects ($n = 1250$), and this patient was not prescribed milnacipran. According to an Australian report, the risk of traffic accidents might not be increased among patients with musculoskeletal disorders due to self-limiting of driving [44]. However, the onset of these disease might have an effect on traffic accidents, so this possibility should be addressed in further studies. We selected the length of the hazard period as 30 days, because it is known that side effects typically appear within the first 2 weeks after the onset of treatment. A sensitivity analysis of the case-crossover design with a 2-week window period was conducted [37]. Generally reduced ORs were observed, although the significant associations for paroxetine, SNRIs, duloxetine, and milnacipran were maintained (results not shown.)

In conclusion, it could not be concluded that entire antidepressant classes contributed to the risk of fatal crashes after controlling for increasing trends in antidepressant utilization; however, we found that the use of paroxetine in the most recent 30 days increased the risk of a fatal road traffic accident. This risk may be explained through the possibility of a drug-induced adverse event, but the possibility of withdrawal syndrome due to low compliance with paroxetine could not be ruled out. For driving patients with depression, prescribing an SSRI other than paroxetine as the first-line drug can be recommended until there is sufficient real-world evidence of the effects of paroxetine on the safety of drivers. Those receiving treatment with paroxetine should be provided education on the risk of withdrawal syndrome. Although milnacipran was also found to be related to fatal crashes, further studies are needed to differentiate whether the risk of fatal traffic accidents observed in milnacipran users was caused by the drug itself, comorbid sleep disorders, or the practice pattern.

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Compliance with ethical standards

Conflict of interest The authors declared no conflict of interest.

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