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ORIGINAL ARTICLE

Antidepressants and the risk of hyponatremia: A multi-institutional cohort study using observational medical outcomes partnership—Common Data Model

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Aim: Hyponatremia is a common yet potentially serious adverse event associated with antidepressants. Identifying the antidepressant class with the least risk of hyponatremia would improve patient safety.

Methods: Using electronic medical records from 15 hospitals standardized into Observational Medical Outcomes Partnership Common Data Model (2003–2023), we identified patients diagnosed with depression who initiated antidepressants, including selective serotonin reuptake inhibitor (SSRI), serotonin–norepinephrine reuptake inhibitor (SNRI), tricyclic antidepressants (TCA) or others (agomelatine, bupropion, mirtazapine, moclobemide and trazodone) for at least 30 days. The index date was defined as the first antidepressant prescription, and four mutually exclusive cohorts were constructed based on the antidepressant class prescribed on index date. Each cohort was compared with all other antidepressants. The primary outcome was incident hyponatremia (serum sodium <135 mmol/L) within the first 180 days. After propensity score stratification, hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using Cox proportional hazards regression. Fixed-effect meta-analysis was used to pool the results from each site.

Results: We identified 17 895 (42.6%) patients in SSRI, 7395 (17.6%) in SNRI, 5424 (12.9%) in TCA and 11 322 (26.9%) in other group. The risk of hyponatremia increased within 180 days after SSRI initiation (HR 1.18, 95% CI 1.01–1.38)

Kyungyeon Jung, Ju Hwan Kim and Da Eun Hyeon contributed equally to this work.

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compared with all other depressants, with a higher risk in patients aged ≥60 years (1.29, 1.06–1.57). No significant association was found for SNRIs (1.05, 0.87–1.27), TCAs (1.03, 0.84–1.26) or other (0.90, 0.77–1.06).

Conclusion: Close monitoring of serum sodium levels is essential for SSRI users, especially those aged ≥60 years.

KEYWORDS

antidepressant, common data model, hyponatremia, SNRI, SSRI, TCA

1 | INTRODUCTION

Depression is a major public health concern with profound implications for both individual well-being and socioeconomic systems. According to the Global Burden of Disease Study, approximately 290 million individuals were affected by depression in 2019,[1] with its prevalence increasing by 32.0% following the COVID-19 pandemic.[2] Antidepressants are essential for managing depressive symptoms and preventing relapse, and their use has increased alongside the growing burden of depression. However, despite their therapeutic benefits, antidepressants are associated with several adverse effects, including hyponatremia.

Hyponatremia is a relatively common electrolyte abnormality, in which the sodium concentration in the blood decreases to below 135 mmol/L.[3] While mild cases of hyponatremia may be asymptomatic, severe cases may potentially lead to life-threatening complications, including seizures, coma, cerebral edema and even death.[4] Several studies have reported an increased risk of hyponatremia across all classes of antidepressants, with particularly high rates observed for selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs).[5–11] Furthermore, previous studies have also observed a higher risk of hyponatremia in elderly antidepressant users.[12,13] However, the results were heterogeneous due to inconsistencies in study designs, data sources, antidepressant classes analysed, study populations and follow-up durations. Furthermore, previous studies lacked longitudinal data on serum sodium levels, limiting the assessment of changes over time.

Given the clinical benefits of antidepressant therapy, identifying the drug class associated with the lowest risk of hyponatremia is crucial to guide clinical decision-making and enhance patient safety. Therefore, our study utilized electronic medical records (EMRs) from 15 hospitals in South Korea, standardized into the Observational Medical Outcomes Partnership–Common Data Model (OMOP-CDM), to evaluate the risk of hyponatremia during the first 180 days following antidepressant initiation.

What is already known about this subject

- Some antidepressants have been consistently linked to an increased risk of hyponatremia, with older adults being especially vulnerable.
- Identifying the antidepressant class with the lowest risk of hyponatremia is essential to support safer clinical decision-making.

What this study adds

- SSRIs are associated with a higher risk of hyponatremia compared with all other antidepressants, especially in patients aged 60 and older.
- Close monitoring of serum sodium is crucial during the early phase of SSRI treatment in older adults.

2 | METHODS

2.1 | Study design and data sources

We conducted a multi-institutional, retrospective cohort study using EMRs from 15 secondary or tertiary hospitals in South Korea from 1 January 2003 to 31 December 2023. The EMRs include records of diagnoses, medications, procedures, and laboratory test values. The records are de-identified and standardized using OMOP-CDM Version 5.3 and validated,[14,15] enabling accessibility through the Federated E-health Big Data for Evidence Renovation Network in Korea (FEEDER-NET).[16,17] Diagnosis records were coded using the Systematized Nomenclature of Medicine (SNOMED)[18] and mapped to the International Classification of Diseases, Tenth Revision, Clinical Modification. Prescription records were coded by their ingredients using RxNorm terminology[19] and classified according to hierarchies such as the Anatomical Therapeutic Chemical classification. Laboratory test values are coded using Logical Observation Identifiers Names and Codes (LOINC).

Distributed network analyses were performed, with each data provider conducting the analysis locally within their firewall. Prespecified statistical results, excluding patient-level information, were shared for database-level meta-analysis. The participating institutions included Ajou University Hospital, Bucheon Sejong Hospital, Daegu Catholic University Hospital, Ewha Womans University Medical Center, Gyeongsang National University Hospital, Incheon Sejong Hospital, Kangdong Sacred Heart Hospital, Kangwon National University Hospital, Keimyung University Dongsan Hospital, Kyung Hee University Hospital at Gangdong, Kyung Hee University Medical Center, Soonchunhyang University Cheonan Hospital, Soonchunhyang

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University Gumi Hospital, Soonchunhyang University Seoul Hospital and Wonkwang University Hospital.

2.2 | Study population and exposures

We included patients aged 18 to 99 years who were diagnosed with depression and newly initiated antidepressants in either inpatient or outpatient settings between 1 January 2003 and 30 December 2023, with continuous use for at least 30 days. Depression included organic mood disorder of the depressed type, depressive disorder, bipolar disorder, and adjustment disorder with depressed mood. The index date was defined as the date of the first antidepressant prescription during the study period. To identify new users and ensure a comprehensive assessment of baseline characteristics, patients were required to have at least 180 days of medical records prior to the index date. Additionally, only patients with normal sodium levels before the index date were included. The cohort study schematic is presented in Figure S1.

The antidepressants that remained authorized for use between 1 January 2021 and 31 December 2023 were included in our study: SSRIs (citalopram, escitalopram, fluoxetine, paroxetine and sertraline), SNRIs (desvenlafaxine, duloxetine and venlafaxine), tricyclic antidepressants (TCAs; amitriptyline, amoxapine, clomipramine, doxepin, imipramine and nortriptyline) and others (agomelatine, bupropion, mirtazapine, moclobemide and trazodone). We created four mutually exclusive cohorts based on the antidepressant class prescribed on the index date: SSRI, SNRI, TCA and other. Each cohort was compared with the respective 'All other depressants' group, which included all antidepressant classes except the one being analysed. For example, the SSRI group was compared with the 'All other depressants' group, consisting of patients prescribed SNRIs, TCAs and others. Four comparisons were made: SSRIs *vs*. All other antidepressants, SNRIs *vs*. All other antidepressants, TCAs *vs*. All other antidepressants and other *vs*. All other antidepressants. Detailed information on the codes used to define depression and antidepressants are presented in Table S1.

2.3 | Outcomes and follow-up

The primary outcome was incident hyponatremia and severe hyponatremia within the first 180 days after antidepressant initiation. Hyponatremia was defined as a serum sodium level <135 mmol/L, and severe hyponatremia was defined as a serum sodium level <125 mmol/L. Patients were followed from the index date until the earliest of outcome occurrence, intensive care unit admission, prescription of a different antidepressant class, last observation in the database or death.

2.4 | Statistical analysis

For each comparison, descriptive statistics were used to summarize participants' characteristics. Demographic factors, including age groups (18–39, 40–59 and ≥60 years) and sex were assessed on the index date, while the Charlson Comorbidity Index (CCI) was evaluated during the 180 days prior to the index date. Baseline characteristics were presented as means for CCI and frequency with proportions for categorical variables.

To address potential confounding, we applied propensity score (PS) stratification using five strata. The PS, which represents the probability of receiving the antidepressant of interest compared to all other antidepressants, was estimated using a logistic regression model, with age group, sex and CCI as independent variables. Covariate balance between the two groups was assessed using absolute standardized mean differences (aSMDs), with values below 0.1 indicating an acceptable balance.

Incidence rates (IRs) per 1000 person-years were estimated, and hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using Cox proportional hazards regression models. After analysing 15 databases using the same R analysis code, we conducted fixed-effect meta-analyses to derive summary HRs and 95% CIs.[20,21]

Additionally, subgroup analyses stratified by age groups (18–39, 40–59 and ≥60 years) were conducted. To assess the robustness of the main findings, sensitivity analyses were performed by varying the outcome assessment period from 180 days to 30 days, 60 days and 90 days. Additional sensitivity analyses were also performed, including adjustment for a range of comedications used during the 180 days before the index date and restricting the study population to individuals who had at least one blood test during the 180-day follow-up period.

2.5 | Nomenclature for targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in (http://www.guidetopharmacology.org), the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY, and are permanently archived in the Concise Guide to PHARMACOLOGY 2021/22.

3 | RESULTS

3.1 | Baseline characteristics

Among 64 185 patients with newly prescribed antidepressants from 15 sites, 42 036 eligible patients were included after PS stratification. We identified 17 895 (42.6%) patients in SSRI, 7395 (17.6%) in SNRI, 5424 (12.9%) in TCA and 11 322 (26.9%) in other groups (Figure 1). Tables 1 and S2 show the baseline characteristics of the study population before and after PS stratification. Before PS stratification, the mean CCI was higher in the SSRI (1.1), SNRI (1.1) and TCA (1.2) groups compared to their respective all other antidepressant groups. After PS stratification, baseline covariates were well-balanced between the groups. The study population had a higher proportion of female patients across all antidepressant classes, with females comprising 66.5% in SSRI group, 65.9% in SNRI group, 66.5% in TCA group and 62.7% in group receiving other antidepressants. The majority of patients were over 60 years old, comprising 53.6%, 48.5%, 51.6% and 52.3% in the SSRI, SNRI, TCA and other groups, respectively.

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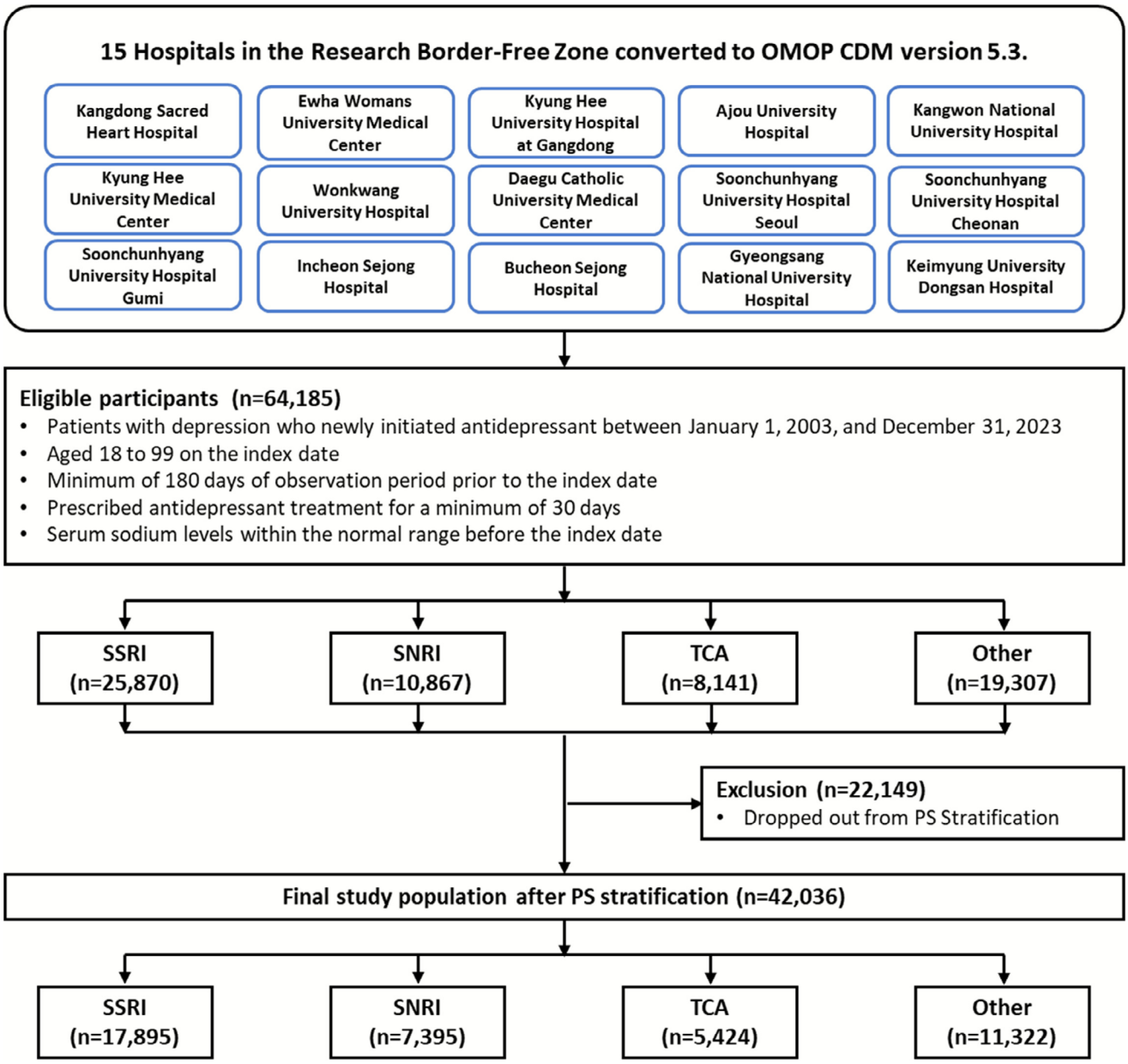


FIGURE 1 Flow chart of study population. Abbreviations: PS, propensity score; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

3.2 | Antidepressants and risk of hyponatremia

During the first 180 days after antidepressant initiation, a total of 425 (2.4%) hyponatremia events were observed in SSRI group, 156 (2.1%) in SNRI group, 120 (2.2%) in TCA group and 243 (2.1%) in group receiving other antidepressants. The corresponding IRs were 49.0 for SSRIs, 43.5 for SNRIs, 45.6 for TCAs and 44.2 for other antidepressants. A significant risk of hyponatremia was observed in SSRI group compared with all other antidepressants, with an HR of 1.18 (95% CI 1.01–1.38). No significant risks of hyponatremia were observed for SNRI (HR 1.05, 95% CI 0.87–1.27), TCA (1.03, 0.84–1.26) and other groups (0.90, 0.77–1.06) (Table 2).

For severe hyponatremia, a total of 43 events (0.2%) were identified in SSRI group, 11 events (0.1%) in SNRI group, 8 events (0.1%) in TCA group and 11 events (0.1%) in group receiving other antidepressants within the first 180 days following treatment initiation. The corresponding IRs per 1000 person-years were 4.9 for SSRIs, 2.9 for SNRIs, 3.0 for TCAs and 2.0 for other antidepressants. No significant association was observed, with HRs of 1.38 (0.61–3.16) for SSRI, 1.51 (0.68–3.37) for SNRI, 1.58 (0.66–3.79) for TCA and 0.58 (0.23–1.49) for other groups, respectively (Table 2).

3.3 | Subgroup and sensitivity analyses

In subgroup analyses stratified by age groups, TCA group had a higher risk in patients aged 18–39 (HR 2.64, 95% CI 1.18–5.90), while SSRI

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TABLE 1 Baseline characteristics of study population after propensity score stratification.

Baseline characteristics	SSRI vs. all other AD			SNRI vs. all other AD			TCA vs. all other AD			Other vs. all other AD		
	SSRI	All other AD[a]	aSMD	SNRI	All other AD[a]	aSMD	TCA	All other AD[a]	aSMD	Other[b]	All other AD[a]	aSMD
No. patients	17 895	14 528		7395	24 189		5424	27 930		11 322	19 197	
Age group, *n* (%)												
18–39	3214 (18.0)	2653 (18.3)	0.001	1404 (19.0)	4278 (17.6)	0.001	873 (16.1)	4676 (16.7)	0.001	2072 (18.3)	3359 (17.5)	0.001
40–59	5082 (28.4)	4077 (28.1)	0.001	2400 (32.5)	7368 (30.5)	0.001	1752 (32.3)	8268 (29.6)	0.001	3324 (29.4)	5439 (38.3)	0.001
≥60	9599 (53.6)	7798 (53.6)	0.001	3591 (48.5)	12 543 (51.9)	0.002	2799 (51.6)	14 986 (53.7)	0.001	5926 (52.3)	10 399 (54.2)	0.002
Sex, *n* (%)			0.01			0.003			0.002			0.003
Male	5997 (33.5)	4939 (34.0)		2525 (34.1)	8461 (35.0)		1818 (33.5)	9434 (33.8)		4225 (37.3)	7059 (36.8)	
Female	11 898 (66.5)	9589 (66.0)		4870 (65.9)	15 728 (65.0)		3606 (66.5)	18 496 (66.2)		7097 (62.7)	12 138 (63.2)	
CCI, mean	1.1	1.0	0.08	1.0	1.0	0.05	1.1	1.0	0.07	1.0	1.0	0.06

Abbreviations: AD, antidepressant; aSMD, absolute standardized mean difference; CCI, Charlson Comorbidity Index; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

[a]All other AD includes all classes of antidepressants except for the specific class being analysed (e.g., for SSRI vs. All other AD, 'All other AD' refers to a group of patients taking all classes of antidepressants other than SSRIs).

[b]Other includes agomelatine, bupropion, mirtazapine, moclobemide and trazodone.

group had a higher risk in those aged 60 and older (1.29, 1.06–1.57) compared with all other antidepressants. Other group was associated with a decreased risk in patients aged 60 and older (0.81, 0.66–0.99). Other subgroup analyses remained consistent with the main findings. Results for subgroup analyses are shown in Table 3.

Figure 2 shows the results from the sensitivity analyses. Consistent with the main findings, SSRI use was associated with a significant increased risk for hyponatremia compared with all other antidepressants. The HRs were 1.39 (1.06–1.82) in the first 30 days, 1.32 (1.07–1.64) in the first 60 days and 1.21 (1.00–1.46) in the first 90 days following SSRI initiation. In contrast, other group exhibited a significantly decreased risk, with the HRs of 0.75 (0.56–1.00), 0.79 (0.62–0.99) and 0.79 (0.65–0.97) over the respective follow-up periods. Other analyses yielded results consistent with the main findings (Table S3). In the sensitivity analysis that additionally adjusted for comedications in the PS model, the findings remained directionally consistent with the main results, with the highest point estimate observed for SSRIs compared with all other antidepressants. HRs were 1.10 (0.93–1.29) for SSRIs, 0.63 (0.51–0.77) for SNRIs, 0.81 (0.65–1.00) for TCAs and 0.54 (0.45–0.65) for other antidepressants, each relative to all other antidepressants (Table S4). The sensitivity analysis restricting the population to individuals who underwent a blood test during the 180-day follow-up period yielded results similar to the main findings. Compared with all other antidepressants, HRs were 1.13 (0.96–1.32) for SSRIs, 1.10 (0.92–1.33) for SNRIs, 0.95 (0.75–1.19) for TCAs and 0.87 (0.72–1.04) for other antidepressants (Table S5).

4 | DISCUSSION

This retrospective cohort study utilized data from the OMOP-CDM database across 15 hospitals in South Korea to evaluate the risk of hyponatremia associated with different classes of antidepressants during the first 180 days of treatment. No significant association was found for SNRIs, TCAs or other antidepressants within the first 180 days of use. However, SSRIs were associated with a significantly increased risk of hyponatremia compared with all other antidepressants. This elevated risk was especially pronounced among patients aged 60 years and older. Notably, the highest incidence of hyponatremia occurred within the first 30 days of SSRI treatment initiation, with the risk gradually declining over time.

Antidepressants have been associated with increased secretion of anti-diuretic hormone (ADH), contributing to the development of syndrome of inappropriate anti-diuretic hormone secretion (SIADH), which impairs water excretion and leads to hyponatremia. The underlying mechanism of SIADH has been linked to effects of serotonin on 5-hydroxytryptamine (5-HT) receptors—primarily **5-HT$_{2C}$**, 5-HT4 and **5-HT$_7$**—as well as effects of norepinephrine on α1-adrenergic receptors, both of which can stimulate ADH secretion.[22] Additionally, recent evidence suggests that SSRIs may enhance renal water reabsorption independently of ADH. Specifically, sertraline has been shown to activate **vasopressin V2 receptors**, increasing aquaporin-2 expression in renal collecting ducts, thereby promoting water retention.[23]

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TABLE 2 Risk of hyponatremia and severe hyponatremia in the first 180 days following antidepressant initiation.

		Hyponatremia			Severe hyponatremia		
AD drugs	**Patients**	**Event (%)**	**IR/1000PY**	**HR (95% CI)**	**Event (%)**	**IR/1000PY**	**HR (95% CI)**
SSRI *vs.* all other AD							
SSRI	17 895	425 (2.4)	49.0	1.18 (1.01–1.38)	43 (0.2)	4.9	1.38 (0.61–3.16)
All other AD[a]	14 528	280 (1.9)	39.6	Reference	12 (0.1)	1.7	Reference
SNRI *vs.* all other AD							
SNRI	7395	156 (2.1)	43.5	1.05 (0.87–1.27)	11 (0.1)	2.9	1.51 (0.68–3.37)
All other AD[a]	24 189	531 (2.2)	45.2	Reference	44 (0.2)	3.7	Reference
TCA *vs.* all other AD							
TCA	5424	120 (2.2)	45.6	1.03 (0.84–1.26)	8 (0.1)	3.0	1.58 (0.66–3.79)
All other AD[a]	27 930	615 (2.2)	45.3	Reference	54 (0.2)	3.9	Reference
Other[b] *vs.* all other AD							
Other[b]	11 322	243 (2.1)	44.2	0.90 (0.77–1.06)	11 (0.1)	2.0	0.58 (0.23–1.49)
All other AD[a]	19 197	445 (2.3)	47.8	Reference	36 (0.2)	6.5	Reference

Abbreviations: AD, antidepressant; CI, confidence interval; HR, hazard ratio; IR, incidence rate; PY, person-years; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

[a]All other AD includes all classes of antidepressants except for the specific class being analysed (e.g., for SSRI *vs.* all other AD, 'All other AD' refers to a group of patients taking all classes of antidepressants other than SSRIs).

[b]Other includes agomelatine, bupropion, mirtazapine, moclobemide and trazodone.

TABLE 3 Subgroup analyses for risk of hyponatremia and severe hyponatremia in the first 180 days following antidepressant initiation.

		Hyponatremia			Severe hyponatremia		
AD drugs	**Patients**	**Events (%)**	**IR/1000PY**	**HR (95% CI)**	**Events (%)**	**IR/1000PY**	**HR (95% CI)**
Aged 18–39 years							
SSRI	3486	32 (0.9)	18.8	0.68 (0.36–1.30)	1 (0.0)	0.6	-
SNRI	1548	19 (1.2)	25.3	1.83 (0.94–3.56)	1 (0.0)	1.3	2.10 (0.08–53.05)
TCA	823	11 (1.3)	30.1	2.64 (1.18–5.90)	0	-	-
Other[a]	2252	25 (1.1)	25.5	1.68 (0.82–3.46)	1 (0.0)	0.9	-
Aged 40–59 years							
SSRI	5569	86 (1.5)	31.7	1.01 (0.72–1.40)	11 (0.2)	4	0.78 (0.08–7.69)
SNRI	2843	32 (1.1)	23.1	0.93 (0.60–1.43)	0	-	-
TCA	2048	36 (1.8)	36.3	1.28 (0.86–1.90)	4 (0.2)	4	3.78 (0.64–22.48)
Other[a]	3738	64 (1.7)	35.2	1.05 (0.74–1.48)	4 (0.1)	2.2	2.59 (0.17–38.75)
Aged ≥60 years							
SSRI	10 300	305 (3.0)	69.7	1.29 (1.06–1.57)	33 (0.3)	7.4	1.16 (0.46–2.92)
SNRI	3209	103 (3.2)	68.9	1.15 (0.92–1.44)	9 (0.3)	5.9	2.30 (0.87–6.08)
TCA	2959	79 (2.7)	55.4	0.96 (0.75–1.23)	5 (0.2)	-	1.39 (0.45–4.25)
Other[a]	5859	160 (2.7)	56.5	0.81 (0.66–0.99)	6 (0.1)	2.1	0.53 (0.19–1.52)

Abbreviations: AD, antidepressant; CI, confidence interval; HR, hazard ratio; IR, incidence rate; PY, person-years; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

[a]All other AD includes all classes of antidepressants except for the specific class being analysed (e.g., for SSRI *vs.* all other AD, 'All other AD' refers to a group of patients taking all classes of antidepressants other than SSRIs).

[b]Other AD includes agomelatine, bupropion, mirtazapine, moclobemide and trazodone.

Given these biological mechanisms, SSRIs have been consistently associated with hyponatremia in previous studies.[11,24–27] Consistently, a significantly increased risk of hyponatremia was observed following SSRI use when compared with all other antidepressants. However, according to a recent study from the Korean Medication Algorithm Project for Depressive Disorder in 2021, escitalopram was identified as the treatment of choice for mild-to-moderate depressive episodes.[28] Between 2009 and 2016, SSRIs were the most frequently prescribed

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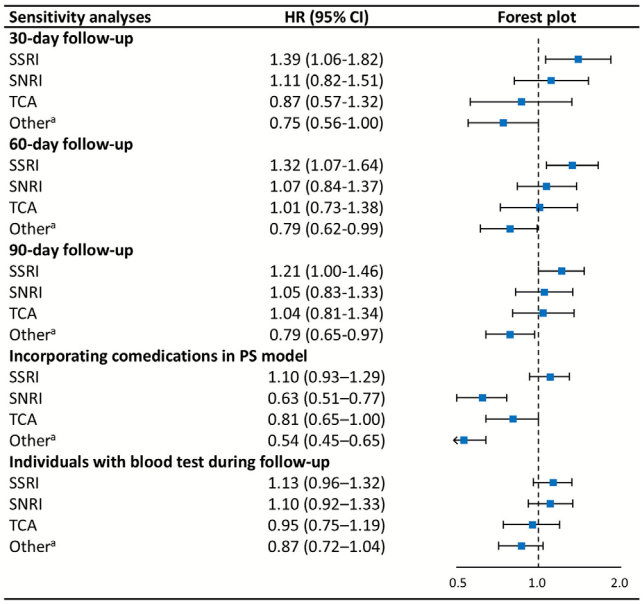


FIGURE 2 Sensitivity analyses for risk of hyponatremia associated with antidepressants. Abbreviations: CI, confidence interval; HR, hazard ratio; PS, propensity score; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant. [a]Other AD includes agomelatine, bupropion, mirtazapine, moclobemide and trazodone.

(35.6%), followed by TCAs (28.1%), SNRIs (6.5%) and other antidepressants (29.8%). While SSRIs are widely recommended as first-line treatments for depression, physicians must remain vigilant about the potential risk of hyponatremia, particularly following SSRI initiation.

Our study did not identify a significant association between SNRIs and hyponatremia compared with all other antidepressants. However, a recent meta-analysis reported slightly higher event rates of hyponatremia following SNRI use (venlafaxine, duloxetine and milnacipran) at 7.44%, compared to SSRIs (fluoxetine, paroxetine, sertraline, escitalopram, citalopram and fluvoxamine) at 5.59%. Additionally, SNRIs were found to be more likely to be associated with hyponatremia than SSRIs (odds ratio: 1.29, 95% CI 1.12–1.49).[9] Furthermore, a retrospective cohort study from the All of Us Research Program observed a higher risk of hyponatremia in duloxetine users compared to sertraline users (HR 1.37, 95% CI 1.19–1.58).[5] While previous studies vary in terms of the medications, comparators and study populations, further investigation into the potential risk of hyponatremia with SNRIs is warranted, particularly in light of the potential mechanisms through which SNRIs may contribute to hyponatremia.

In addition, our study found that the risk of hyponatremia was lower in users of agomelatine, bupropion, mirtazapine, moclobemide, and trazodone compared to all other antidepressants. Previous studies have suggested that bupropion and mirtazapine may be safer options than SSRIs or SNRIs, as they have not been commonly associated with SIADH.[29–31] However, a recent meta-analysis reported that monoamine oxidase inhibitors (MAOIs) had the highest odds ratio for hyponatremia (3.8, 95% CI 1.60–8.97).[10] Since we included various antidepressant classes in other group, including noradrenergic and specific serotonergic antidepressants, MAOIs, serotonin antagonists and reuptake inhibitors, and norepinephrine/dopamine-reuptake inhibitors, further studies on the risk of hyponatremia for each class are needed.

In subgroup analyses, patients aged 60 and older who initiated SSRIs exhibited a significantly higher risk of hyponatremia compared with all other depressants. This finding is likely explained by age-related physiological changes, such as increased sensitivity to ADH and reduced kidney function, which impair free water excretion.[32] These results highlight the need for careful monitoring of hyponatremia risk when prescribing SSRIs to elderly patients. Moreover, as elderly individuals are more likely to have conditions that are risk factors for hyponatremia, such as heart failure, severe kidney disease or cirrhosis, the use of SSRIs in high-risk patients should be carefully considered.[33–35] Interestingly, we observed a significantly increased risk of hyponatremia with TCAs in patients aged 18–39 years compared with all other antidepressants. This is particularly noteworthy, as the antidepressant class associated with a higher risk of hyponatremia appears to vary across different age groups. The exact biological mechanisms by which the anticholinergic and adrenergic effects of TCAs contribute to hyponatremia in young adults remain unclear, emphasizing the need for further research to better understand this association in patients under 40 years of age.

Sensitivity analyses varying the outcome assessment period showed consistent results with the main findings. For SSRI, a significantly increased risk of hyponatremia was observed compared with all other antidepressants, with the risk decreasing over time. Previous studies have also reported the highest risk of hyponatremia was observed within the first 2 weeks to 30 days of treatment. This may support the assumed SIADH mechanism, where ADH distribution and its effects occur within hours.[36] However, the overall trend showed a decline in hyponatremia risk over time, variations in event incidence were noted across different antidepressant classes.[5] Therefore, long-term risks should be further investigated to fully understand the temporal risk profile of hyponatremia.

Our study has several strengths. First, we utilized a multi-institutional database converted into the OMOP-CDM format, which ensured a large study population and high validity in serum sodium measurements. We also compared each class of antidepressants with all others, potentially guiding optimal treatment selection for patients at high risk of hyponatremia. Importantly, we focused on clinically significant hyponatremia, including cases with serum sodium levels <135 and <125 mmol/L, during the first 180 days following antidepressant initiation. Although not statistically significant, elevated point estimates for severe hyponatremia were observed with SSRI, SNRI and TCA use compared with all other antidepressants. Given the potential mechanisms linking SIADH to severe hyponatremia, caution is warranted, and the risk should not be entirely dismissed.

However, several limitations should be considered. First, due to the nature of observational studies, there is a possibility of unmeasured confounding. Variables such as education level, socioeconomic status and lifestyle factors were not accounted for. Second, we included only patients with at least one recorded serum sodium level,

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which may introduce selection bias. However, this study utilized EMRs from secondary and tertiary hospitals, where blood tests are often routinely performed in departments that frequently treat patients with depression. Additionally, since SSRIs are a commonly prescribed and generally safe option for patients with renal failure,[37,38] this could also contribute to selection bias. Third, although an ideal randomized clinical trial would routinely monitor serum sodium after the index date, our study did not require blood testing during the 180-day follow-up, which may have led to underestimation of hyponatremia events. Nevertheless, this underestimation is expected to be non-differential between treatment groups. In addition, a sensitivity analysis restricting the study population to individuals who underwent blood testing during the 180-day follow-up yielded results that were consistent with the main findings. Nonetheless, these results should be interpreted with caution because the target study population was altered. Fourth, we did not conduct direct comparisons of individual antidepressants, meaning that the other group may include medications with different risks of hyponatremia due to diverse biological mechanisms. Fourth, although pooled HRs and CIs suggested a significant association between SSRIs and hyponatremia, the results may vary across individual databases. To address the inconsistency, likely due to small sample sizes and limited statistical power within each database, we applied a fixed-effects model to mitigate potential biases. Lastly, we used the EMR from 15 secondary and tertiary hospitals participating in the Researcher's Freedom Zone, our findings may not be generalizable to primary care settings, or to healthcare systems outside of South Korea.

In conclusion, our study found a significantly increased risk of hyponatremia associated with SSRIs compared with other antidepressants, particularly in patients aged 60 and older. This finding highlights the need for increased vigilance when prescribing SSRIs to older adults, and close monitoring of serum sodium levels after SSRI initiation is essential, especially during the early phase of treatment. Further research focusing on high-risk subgroups, including older adults, patients with comorbidities, and those taking concomitant medications known to influence sodium balance, is needed to strengthen the clinical evidence base for the safe use of SSRIs. Moreover, investigating the risk of hyponatremia with TCAs in patients under 40, as well as head-to-head comparisons of different antidepressant classes, would provide valuable insights to guide treatment strategies for depression.

AUTHOR CONTRIBUTIONS

Conceptualization: Kyungyeon Jung, Ju Hwan Kim, Da Eun Hyeon, Jeongmoon Ji, Hayun Choi, Dong Yun Lee, Min Woo Kim, Yoonmin Jang, Seonghoon Hwang, Rae Woong Park, Ju-Young Shin. Data curation: Jaehyeong Cho, Seok Young Song, Sang Youl Rhee, Jae Myung Cha, Won-Woo Seo, Chang-Won Jeong, Seung-Jin Kwag, Woo Jin Kim, Jaeuk Hwang, Min-ho Kim. Formal analysis: Da Eun Hyeon, Jeongmoon Ji. Funding acquisition: Rae Woong Park, Ju-Young Shin. Investigation: Da Eun Hyeon, Jeongmoon Ji. Methodology: Kyungyeon Jung, Ju Hwan Kim, Da Eun Hyeon, Jeongmoon Ji, Hayun Choi, Dong Yun Lee, Min Woo Kim, Yoonmin Jang, Seonghoon Hwang, Rae Woong Park, Ju-Young Shin. Writing—original draft: Kyungyeon Jung, Ju Hwan Kim, Da Eun Hyeon. Writing—review and editing: all authors.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

CDM data are designed to support a distributed research network. Thus, access to the data is restricted on internal private networks. Therefore, data are not publicly available.

TRANSPARENCY DECLARATION

The corresponding authors confirm that the manuscript represents an honest, accurate and transparent account of the study's findings.

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