Identifying Antidepressants Less Likely to Cause Hyponatremia: Triangulation of Retrospective Cohort, Disproportionality, and Pharmacodynamic Studies

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Antidepressants are known to cause hyponatremia, but conflicting evidence exists regarding specific antidepressants. To identify antidepressants less likely to cause hyponatremia, we conducted a triangulation study integrating retrospective cohort, disproportionality, and pharmacodynamic studies. In the retrospective cohort study of patients (≥ 60 years) in Nihon University School of Medicine's Clinical Data Warehouse (2004–2020), a significant decrease in serum sodium levels was observed within 30 days after initiation of a selective serotonin reuptake inhibitor (SSRI; mean change −1.00 ± 0.23 mmol/L, $P < 0.001$) or serotonin-noradrenaline reuptake inhibitor (SNRI; −1.01 ± 0.31 mmol/L, $P = 0.0013$), whereas no decrease was found for a noradrenergic and specific serotonergic antidepressant (mirtazapine; +0.55 ± 0.47 mmol/L, $P = 0.24$). Within-class comparison revealed no decrease in serum sodium levels for fluvoxamine (+0.74 ± 0.75 mmol/L, $P = 0.33$) among SSRIs and milnacipran (+0.08 ± 0.87 mmol/L, $P = 0.93$) among SNRIs. In the disproportionality analysis of patients (≥ 60 years) in the Japanese Adverse Drug Event Report database (2004–2020), a significant increase in hyponatremia reports was observed for SSRIs (reporting odds ratio 4.41, 95% confidence interval 3.58–5.45) and SNRIs (5.66, 4.38–7.31), but not for mirtazapine (1.08, 0.74–1.58), fluvoxamine (1.48, 0.94–2.32), and milnacipran (0.85, 0.45–1.62). Finally, pharmacoepidemiological–pharmacodynamic analysis revealed a significant correlation between the decrease in serum sodium levels and binding affinity for serotonin transporter (SERT; $r = −0.84$, $P = 0.02$), suggesting that lower binding affinity of mirtazapine, fluvoxamine, and milnacipran against SERT is responsible for the above difference. Although further research is needed, our data suggest that mirtazapine, fluvoxamine, and milnacipran are less likely to cause hyponatremia.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Antidepressant-induced hyponatremia is a potentially life-threatening adverse effect. However, owing to conflicting evidence regarding specific antidepressants, it is unclear which antidepressants are less likely to cause hyponatremia.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ This study aimed to identify antidepressants that are less likely to cause hyponatremia through triangulation of retrospective cohort, disproportionality, and pharmacodynamic studies.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Mirtazapine, fluvoxamine, and milnacipran are less likely to cause hyponatremia because of (i) no lowering effect on serum sodium levels, (ii) no significant increase in hyponatremia reports, and (iii) lower binding affinity for serotonin transporter capable of explaining (i) and (ii).

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Our study provides clinically useful information for optimizing current antidepressant therapy as well as pharmacologically important insights for developing safer antidepressants in the future.

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Antidepressants are commonly used to treat depression and other disorders in clinical practice. Among the different antidepressants, new-generation antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs), are recommended as first-line treatment because they are believed to be safer than the older tricyclic antidepressants (TCAs). However, recent studies have shown that some adverse effects are more pronounced in new-generation antidepressants.[1,2] Hyponatremia is one such adverse effect, with symptoms ranging from mild lethargy and anorexia to severe seizures and coma.[3,4] As these symptoms overlap with those of depression, antidepressant-induced hyponatremia may go unnoticed and could lead to life-threatening consequences. Therefore, it is clinically important to identify antidepressants that are less likely to cause hyponatremia.

The relationship between antidepressants and hyponatremia has been studied extensively in recent years.[5–10] Some studies have analyzed electronic health records in Britain,[5] Denmark,[6] Canada,[7] and Sweden[8] through retrospective cohort or case-control designs, whereas others have analyzed adverse event reports through drug surveillance[9] or disproportionality methods.[10] Despite these efforts, a consensus for this relationship has not been achieved because of conflicting evidence. For example, some studies have identified a lower risk of hyponatremia for noradrenergic and specific serotonergic antidepressants (NaSSAs; e.g., mirtazapine),[6–9] whereas a recent study using the world's largest spontaneous reporting database found the highest reporting risk of hyponatremia for mirtazapine.[10] Heterogeneity within the same class of antidepressants is also controversial; one population-based cohort study with the largest sample size identified the lowest risk of hyponatremia with escitalopram among SSRIs,[6] whereas other studies found the highest risk of hyponatremia with escitalopram.[5,9] Thus, owing to conflicting evidence regarding specific antidepressants, it is unclear which antidepressants are less likely to cause hyponatremia.

Triangulation is an effective way to resolve conflicting evidence by identifying more reliable evidence through the strategic use of multiple approaches.[11,12] After reviewing the limitations of previous studies, we considered it important for the effect of antidepressants to be (i) evaluated by objective measures, (ii) confirmed by multiple sources, and (iii) supported by plausible mechanisms. In previous studies, the definition of hyponatremia was arbitrary with respect to cutoff values and diagnostic criteria, which might have introduced bias into the objective evaluation of the effect of antidepressants.[3,4] Additionally, most studies have focused on analyzing either electronic health records or adverse event reports, but both sources have limitations in extracting accurate safety information when used alone.[13,14] Moreover, although the involvement of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) in antidepressant-induced hyponatremia is generally accepted, limited studies have examined its molecular mechanisms, resulting in a lack of biologically plausible evidence.[15]

To address the above issues, we designed a triangulation study that integrates (i) a retrospective cohort study of mean changes in serum sodium levels, (ii) a disproportionality analysis of an independent spontaneous reporting database, and (iii) a pharmacodynamic analysis of the responsible target molecules. Using these multiple approaches, we aimed to identify antidepressants that are less likely to cause hyponatremia.

METHODS

Retrospective cohort study in the Nihon University School of Medicine's Clinical Data Warehouse

Data source. The first approach in this triangulation study was a retrospective cohort study using electronic medical records stored in the Nihon University School of Medicine's Clinical Data Warehouse (NUSM's CDW). This database contains demographic, diagnostic, prescription, and laboratory data for both inpatients and outpatients at three hospitals affiliated with NUSM.[16] Diagnoses are coded according to the Japanese Standard Disease Code Master, which is compatible with the International Classification of Diseases, 10th revision (ICD-10). Prescriptions are coded using the Japanese drug coding system, which is mapped to the Anatomical Therapeutic Chemical (ATC) classification. Several epidemiological studies have been previously published evaluating the effects of various drugs on laboratory parameters using NUSM's CDW.[17–20] The experimental protocol was approved by the Ethical Committee of NUSM (approval number: P21-01-0), and the study was conducted in compliance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects of the Ministry of Education, Culture, Sports, Science, and Technology and the Ministry of Health, Labour, and Welfare, Japan.

Study design, exposure, and outcome. This study included elderly Japanese patients (≥ 60 years) whose sodium levels were measured before and after the initiation of antidepressant treatment between November 1, 2004, and July 31, 2020, in NUSM's CDW. Among the different antidepressants available in Japan (**Table S1**), the present study focused on new-generation antidepressants as the primary exposure of interest, including the following agents: paroxetine (ATC code: N06AB05), sertraline (N06AB06), fluvoxamine (N06AB08), escitalopram (N06AB10), duloxetine (N06AX21), milnacipran (N06AX17), venlafaxine (N06AX16), mirtazapine (N06AX11), and vortioxetine (N06AX26). After defining the index date as the date of the first prescription for the antidepressant of interest, new users were identified as those who had at least 365 days of continuous observation time before the index date and had not been prescribed any antidepressant before the index date. The primary outcome of interest was the mean change in serum sodium levels, and no cutoff values or diagnostic criteria were set. The advantage of this outcome is that the effect of antidepressants can be objectively evaluated by avoiding potential bias due to the definition of hyponatremia. A potential limitation of this outcome is that its clinical relevance (e.g., symptoms) cannot be evaluated, but this limitation can be overcome by analyzing spontaneous reports (the second approach in this triangulation study). Serum sodium levels were collected within 90 days before the index date and within 30 days after the index date, and the median value was used when multiple measurements were available for the same patient. Patients who were prescribed antidepressants other than the antidepressant of interest within 30 days after the index date were excluded from the study.

The detailed study design and flowcharts are shown in **Figures S1** and **S2**. This study focused on acute changes (within 30 days) as antidepressant-induced hyponatremia occurs shortly after treatment initiation[5,6,8] (confirmed in **Figure S3**). This study focused on elderly patients (≥ 60 years) as antidepressant-induced hyponatremia occurs primarily in elderly patients[3,4] (confirmed in **Figure S4**). Patients were included regardless of indications for antidepressant treatment as they did not modify the effect of antidepressants (**Figure S5**). As a secondary outcome of interest, the effect on urine sodium levels was also evaluated in **Figure S3c**. As a secondary exposure of interest, the effects of older antidepressants were also evaluated in **Figures S7–S9**.

Potential confounders. To adjust for differences in baseline characteristics, we collected information on patient demographics (age and sex), medical history, and medication use in addition to laboratory data of serum sodium levels. Medical history included heart failure (ICD-10 code: I50), kidney failure (N17–N19), liver disease (K70–K77), hypothyroidism (E03 or E06.3), malignancy (C00–C97), previous hyponatremia (E87.1), and adrenal insufficiency (E27) during the 365 days before the index date. Medication use included diuretics (ATC code: C03), antiepileptics (N03), angiotensin-converting enzyme inhibitors (C09A), beta blockers (C07), proton pump inhibitors (A02BC), non-steroidal anti-inflammatory drugs (M01A), anticancer agents (L01), and laxatives (A06A) during the 90 days before the index date. These potential confounders were selected based on known risk factors for antidepressant-induced hyponatremia,[3,4] and the majority (16/18 = 88.9%) were confirmed to contribute to the decrease in serum sodium levels after the initiation of antidepressant treatment (**Figure S6**). Of note, the decrease was significantly exacerbated by concomitant use of other hyponatremia-inducing drugs (e.g., diuretics), which is in accordance with the findings of many studies.[3,4,9]

Statistical analysis. For continuous variables, data were expressed as mean ± SD or standard error of the mean (SEM). Paired *t*-test was used to compare means before and after treatment. Analysis of variance was used to compare means among different treatment groups. Multivariate linear regression and analysis of covariance were used to calculate and compare the estimated marginal means (also known as least square means) adjusted for covariates. For categorical variables, data were expressed as frequency (*n*) and proportion (%). Fisher's exact test was used to compare proportions among different treatment groups. All statistical analyses were performed using R software version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). Only groups with $N \geq 5$ were included in statistical analysis. $P < 0.05$ was considered statistically significant.

Disproportionality analysis of Japanese Adverse Drug Event Report database

Data source. The second approach in this triangulation study was a disproportionality analysis of the Japanese Adverse Drug Event Report (JADER) database. This database contains spontaneous adverse event reports with detailed information on demographics, drugs, reactions, and indications. The advantage of this database is that clinically relevant adverse events worth reporting can be analyzed. A potential limitation of this database is that various reporting biases may affect the estimation of true drug effects, but this limitation can be overcome by analyzing laboratory parameters (the first approach in this triangulation study). Drugs are coded using generic names. Adverse events and indications are coded according to the Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms. The JADER database is publicly available on the website of the Pharmaceuticals and Medical Devices Agency (https://www.pmda.go.jp).

Study design, exposure, and outcome. This study included 366,232 reports of elderly Japanese patients (≥ 60 years) submitted to JADER between January 2004 and March 2020. This study focused on new-generation antidepressants as the primary exposure of interest. The outcome was assessed using the reporting odds ratio for hyponatremia/SIADH (standardized MedDRA query code: 20000141, narrow scope, version 20.1). SIADH and hyponatremia were the most frequently reported adverse events in elderly patients treated with new-generation antidepressants (**Figure S10**). As a secondary exposure of interest, effects of older antidepressants were also evaluated in **Figure S11**.

Potential confounders. Traditional disproportionality analysis is subject to bias due to comorbidities, comedications, and other confounders. To reduce this bias, we applied a high-dimensional propensity score matching method using age, sex, up to 200 comorbidities, and up to 200 comedications. Comorbidities and comedications were selected based on their frequency (≥ 0.1%) and statistical significance of the difference between users and nonusers of the antidepressant of interest ($P < 0.05$ in ascending order; see example in **Table S2**). This strategy was based on a previously published method that successfully reduced confounding bias in spontaneous reports.[21]

Statistical analysis. For comparison between users and nonusers, data were expressed as frequency (*n*) and proportion (%) with 95% Clopper–Pearson's confidence interval (CI). Fisher's exact test was used to compare proportions. For comparison among different treatment groups, data were expressed as reporting odds ratios with 95% Wald's CIs. Cochran's *Q*-test was used to assess the heterogeneity of odds ratios. Logistic regression was used to calculate propensity scores. Matching was performed in a 1:1 ratio using a nearest neighbor algorithm without replacement. All statistical analyses were performed using R software version 3.6.3. Only groups with $N \geq 5$ were included in statistical analysis. $P < 0.05$ was considered statistically significant.

Pharmacoepidemiological–pharmacodynamic analysis

Study design. The third approach in this triangulation study was a pharmacoepidemiological–pharmacodynamic (PE–PD) analysis, which is a novel method for exploring the mechanisms of adverse drug events by combining pharmacoepidemiological results and pharmacodynamic properties.[22] The present study assessed the correlation between mean changes in serum sodium levels or reporting odds ratios for hyponatremia/SIADH and binding affinities to various target molecules. The pKi values (negative logarithm to the base 10 of the inhibition constant Ki) were used as a measure of the strength of binding affinity. Therapeutic drug concentration and protein binding were not considered in this study as recent studies did not support a dose-dependent increase in the risk of antidepressant-induced hyponatremia.[5,7,9] The pKi values used in this study are summarized in **Table S3**. These pKi values were adopted from previous PE–PD studies by Mazhar *et al*.,[10] Nguyen *et al*.,[23] and Siafis *et al*.[24] in this priority order. These studies retrieved human/mouse pKi values from IUPHAR/BPS Guide to PHARMACOLOGY, PDSP Ki database, DrugBank, and ChEMBL and calculated the geometric mean when multiple values were available for the same target. The present PE–PD analysis included the following molecules whose pKi values were available for more than half of the antidepressants investigated in this study: serotonin transporter (SERT); norepinephrine transporter (NET); dopamine transporter (DAT); serotonin 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptors; α_1 and α_2 adrenergic receptors; dopamine D_2 receptor; histamine H_1 receptor; and M_{1-5} muscarinic receptors.

Statistical analysis. Pearson's correlation test was used to assess the linear correlation between two continuous variables. Analyses were weighted by sample size to minimize the influence of outliers. All statistical analyses were performed using R software version 3.6.3. $P < 0.05$ was considered statistically significant.

RESULTS

Retrospective cohort study in NUSM's CDW

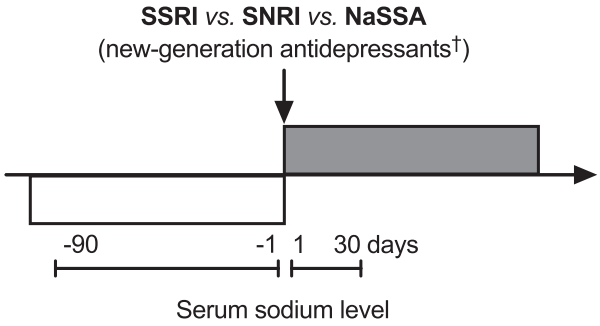
Between-class comparison of new-generation antidepressants. **Figure 1** shows the effect of each class of new-generation antidepressants on serum sodium levels. We compared the mean change in serum sodium levels within 30 days after the initiation of SSRIs ($N = 274$), SNRIs ($N = 171$), or NaSSA (mirtazapine, $N = 46$; **Figure 1a,b**). A significant decrease in serum sodium levels

was observed for SSRIs (mean change −1.00 ± 0.23 mmol/L, $P < 0.001$) and SNRIs (−1.01 ± 0.31 mmol/L, $P = 0.0013$; **Figure 1c**). In contrast, no decrease in serum sodium levels was found for NaSSA (+0.55 ± 0.47 mmol/L, $P = 0.24$). There was a significant difference in the change in serum sodium levels among classes of new-generation antidepressants ($P = 0.03$; **Figure 1d**). Even after adjusting for potential confounders, the difference remained statistically significant ($P = 0.02$; **Figure 1e**).

Within-class comparison of selective serotonin reuptake inhibitors. **Figure 2** shows the effect of each SSRI on serum sodium levels. We compared the mean change in serum sodium levels within 30 days after the initiation of paroxetine ($N = 167$), sertraline ($N = 61$), fluvoxamine ($N = 29$), or escitalopram ($N = 16$; **Figure 2a,b**). A significant decrease in serum sodium levels was observed for paroxetine (mean change −1.44 ± 0.29 mmol/L, $P < 0.001$; **Figure 2c**). Although not statistically significant, a decrease in serum sodium levels was also observed for sertraline (−0.56 ± 0.47 mmol/L, $P = 0.24$) and escitalopram (−1.00 ± 1.01 mmol/L, $P = 0.34$). In contrast, no decrease in serum sodium levels was found for fluvoxamine (+0.74 ± 0.75 mmol/L, $P = 0.33$). There was significant heterogeneity in the change in serum sodium levels among SSRIs ($P = 0.03$; **Figure 2d**). Even after adjusting for potential confounders, the heterogeneity remained statistically significant ($P = 0.02$; **Figure 2e**).

Within-class comparison of serotonin-noradrenaline reuptake inhibitors. **Figure 3** shows the effect of each SNRI on serum sodium levels. We compared the mean change in serum sodium levels within 30 days after the initiation of duloxetine ($N = 128$) or milnacipran ($N = 43$; **Figure 3a,b**). A significant decrease in serum sodium levels was observed for duloxetine (mean change −1.38 ± 0.29 mmol/L, $P < 0.001$; **Figure 3c**). In contrast, no decrease in serum sodium levels was found for milnacipran (+0.08 ± 0.87 mmol/L, $P = 0.93$). There was significant

(a)



(b)

Characteristics	SSRI (*N* = 274)	SNRI (*N* = 171)	NaSSA (*N* = 46)	*P* value
Demographics				
Age (years), mean ± SD	72.7 ± 7.4	74.5 ± 7.4	72.3 ± 6.3	0.03
Female, *n* (%)	143 (52.2)	105 (61.4)	22 (47.8)	0.09
Medical history, *n* (%)				
Heart failure	68 (24.8)	48 (28.1)	11 (23.9)	0.72
Kidney failure	39 (14.2)	22 (12.9)	4 (8.7)	0.66
Liver disease	73 (26.6)	35 (20.5)	12 (26.1)	0.32
Hypothyroidism	46 (16.8)	29 (17.0)	12 (26.1)	0.31
Malignancy	185 (67.5)	119 (69.6)	37 (80.4)	0.21
Previous hyponatremia	14 (5.1)	4 (2.3)	1 (2.2)	0.34
Adrenal insufficiency	7 (2.6)	2 (1.2)	1 (2.2)	0.55
Medication use, *n* (%)				
Diuretics	92 (33.6)	47 (27.5)	12 (26.1)	0.32
Antiepileptics	39 (14.2)	55 (32.2)	11 (23.9)	< 0.001
Angiotensin-converting enzyme inhibitors	23 (8.4)	5 (2.9)	5 (10.9)	0.03
Beta blockers	37 (13.5)	28 (16.4)	9 (19.6)	0.45
Proton pump inhibitors	146 (53.3)	108 (63.2)	26 (56.5)	0.12
Non-steroidal anti-inflammatory drugs	125 (45.6)	86 (50.3)	20 (43.5)	0.56
Anticancer agents	48 (17.5)	38 (22.2)	9 (19.6)	0.47
Laxatives	126 (46.0)	59 (34.5)	25 (54.3)	0.014
Laboratory parameter, mean ± SD				
Baseline serum sodium level (mmol/L)	139.5 ± 3.4	139.8 ± 3.5	139.8 ± 3.8	0.52

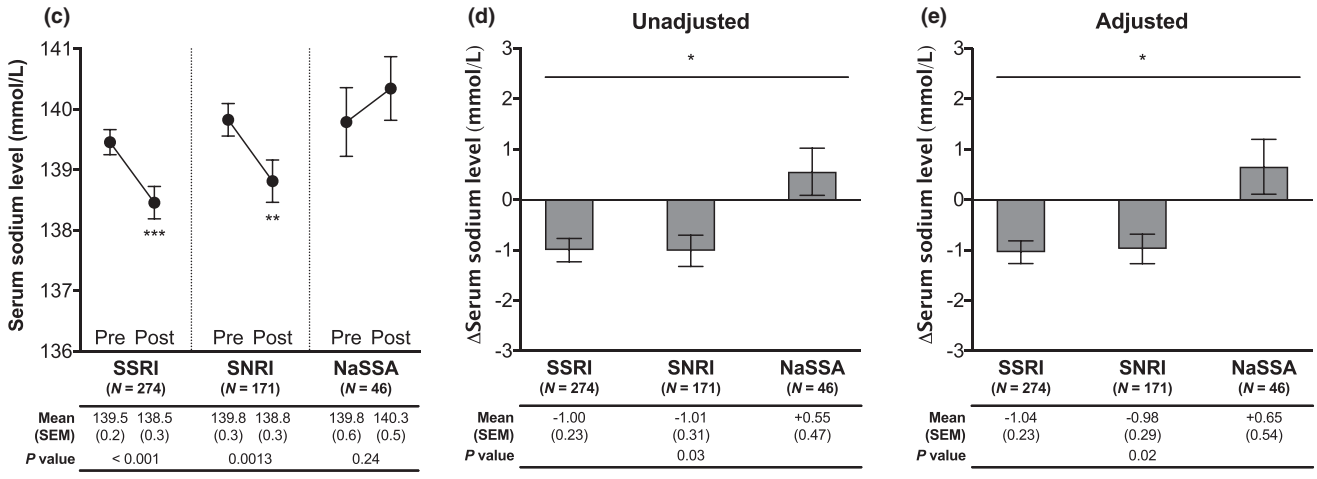
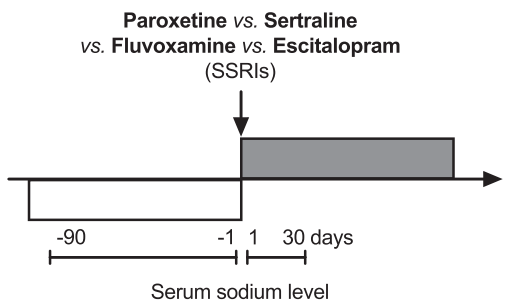


Figure 1 Between-class comparison of the effect of new-generation antidepressants on serum sodium levels. (**a**) Study design. †SMS ($N = 0$) was not included. (**b**) Baseline characteristics. (**c**) Serum sodium levels before and after treatment. (**d**) Change in serum sodium levels during treatment. (**e**) Change in serum sodium levels adjusted for age, sex, medical history, medication use, and baseline serum sodium levels. Data are expressed as mean ± SEM. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. NaSSA, noradrenergic and specific serotonergic antidepressant (mirtazapine); SMS, serotonin modulator and stimulator (vortioxetine); SNRI, serotonin-noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

(a)



(b)

Characteristics	Paroxetine (*N* = 167)	Sertraline (*N* = 61)	Fluvoxamine (*N* = 29)	Escitalopram (*N* = 16)	*P* value
Demographics					
Age (years), mean ± SD	73.1 ± 7.7	72.9 ± 7.6	71.5 ± 6.3	70.2 ± 5.7	0.37
Female, *n* (%)	85 (50.9)	29 (47.5)	19 (65.5)	9 (56.3)	0.42
Medical history, *n* (%)					
Heart failure	48 (28.7)	15 (24.6)	2 (6.9)	2 (12.5)	0.04
Kidney failure	24 (14.4)	9 (14.8)	2 (6.9)	4 (25.0)	0.42
Liver disease	51 (30.5)	12 (19.7)	5 (17.2)	4 (25.0)	0.26
Hypothyroidism	30 (18.0)	12 (19.7)	2 (6.9)	2 (12.5)	0.47
Malignancy	117 (70.1)	42 (68.9)	12 (41.4)	13 (81.3)	0.02
Previous hyponatremia	9 (5.4)	3 (4.9)	1 (3.4)	1 (6.3)	1.00
Adrenal insufficiency	1 (0.6)	4 (6.6)	1 (3.4)	1 (6.3)	0.02
Medication use, *n* (%)					
Diuretics	63 (37.7)	17 (27.9)	8 (27.6)	3 (18.8)	0.27
Antiepileptics	23 (13.8)	12 (19.7)	1 (3.4)	3 (18.8)	0.16
Angiotensin-converting enzyme inhibitors	13 (7.8)	8 (13.1)	2 (6.9)	0 (0.0)	0.43
Beta blockers	25 (15.0)	8 (13.1)	3 (10.3)	1 (6.3)	0.86
Proton pump inhibitors	94 (56.3)	35 (57.4)	14 (48.3)	3 (18.8)	0.03
Non-steroidal anti-inflammatory drugs	79 (47.3)	29 (47.5)	12 (41.4)	4 (25.0)	0.37
Anticancer agents	31 (18.6)	10 (16.4)	3 (10.3)	4 (25.0)	0.61
Laxatives	78 (46.7)	27 (44.3)	12 (41.4)	9 (56.3)	0.79
Laboratory parameter, mean ± SD					
Baseline serum sodium level (mmol/L)	139.5 ± 3.3	139.3 ± 3.0	139.4 ± 4.8	139.5 ± 3.8	0.98

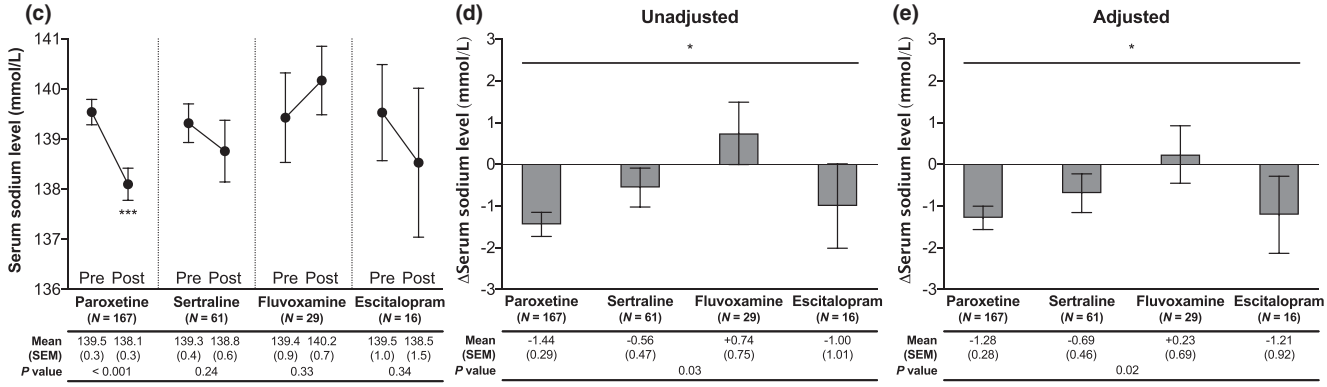


Figure 2 Within-class comparison of the effect of selective serotonin reuptake inhibitors on serum sodium levels. (**a**) Study design. (**b**) Baseline characteristics. (**c**) Serum sodium levels before and after treatment. (**d**) Change in serum sodium levels during treatment. (**e**) Change in serum sodium levels adjusted for age, sex, medical history, medication use, and baseline serum sodium levels. Data are expressed as mean ± SEM. *$P < 0.05$, ***$P < 0.001$. SSRI, selective serotonin reuptake inhibitor.

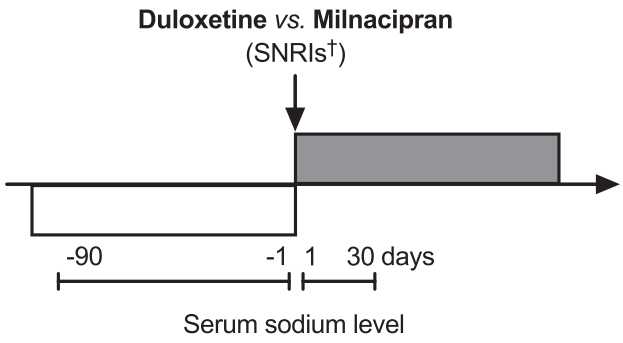
heterogeneity in the change in serum sodium levels among SNRIs ($P = 0.04$; **Figure 3d**). Even after adjusting for potential confounders, the heterogeneity remained statistically significant ($P = 0.04$; **Figure 3e**).

Effects of older antidepressants. Effects of older antidepressants on serum sodium levels are summarized in **Figures S7–S9**. A significant decrease in serum sodium levels was observed for TCAs (mean change −0.72 ± 0.22 mmol/L, $P = 0.0014$; **Figure S7**). Although not statistically significant, a decrease in serum sodium levels was also observed for a serotonin antagonist and reuptake inhibitor (trazodone; −0.61 ± 0.39 mmol/L, $P = 0.12$). In contrast, no decrease in serum sodium levels was found for tetracyclic antidepressants (TeCAs; +0.05 ± 0.44 mmol/L, $P = 0.91$). Within-class comparison of TCAs showed a significant decrease in serum sodium levels for amitriptyline (−0.88 ± 0.34 mmol/L, $P = 0.012$; **Figure S8**). A similar trend was also observed for nortriptyline (−0.37 ± 0.30 mmol/L, $P = 0.23$), clomipramine (−1.50 ± 2.02 mmol/L, $P = 0.49$), and amoxapine (−4.30 ± 1.63 mmol/L, $P = 0.06$). Such a decrease was not observed for imipramine (+0.86 ± 0.58 mmol/L, $P = 0.16$). There was significant heterogeneity in the change in serum sodium levels among TCAs before ($P = 0.04$) and after ($P = 0.04$) adjustment for potential confounders. On the other hand, no significant decrease or heterogeneity was observed among TeCAs (**Figure S9**).

Disproportionality analysis of JADER

We further performed a disproportionality analysis of JADER to confirm the above results in an independent database (**Figure 4**). We compared the relationship between new-generation antidepressants and hyponatremia/SIADH reports after propensity score matching (**Figure 4a**). Between-class comparison of new-generation antidepressants revealed a significant increase in hyponatremia/SIADH reports for SSRIs (reporting odds ratio 4.41, 95% CI 3.58–5.45) and SNRIs (5.66, 4.38–7.31) but not for NaSSA (1.08, 0.74–1.58; **Figure 4b,c**). Within-class comparison of SSRIs revealed a significant increase in hyponatremia/SIADH reports for paroxetine (4.27, 3.19–5.71), sertraline (4.06, 2.70–6.11), and escitalopram (5.14, 3.02–8.75) but not for fluvoxamine (1.48, 0.94–2.32; **Figure 4d,e**). Within-class comparison of SNRIs revealed a significant increase in hyponatremia/SIADH reports for duloxetine (7.81, 5.76–10.60) but not for milnacipran (0.85, 0.45–1.62; **Figure 4f,g**). These results were consistent with the results obtained in NUSM's CDW. On the other hand, none of the older antidepressants showed a significant increase in hyponatremia/SIADH reports (**Figure S11**), which were slightly different from the results in NUSM's CDW.

(a)



(b)

Characteristics	Duloxetine (*N* = 128)	Milnacipran (*N* = 43)	*P* value
Demographics			
Age (years), mean ± SD	74.5 ± 7.4	74.5 ± 7.8	0.99
Female, *n* (%)	77 (60.2)	28 (65.1)	0.59
Medical history, *n* (%)			
Heart failure	31 (24.2)	17 (39.5)	0.08
Kidney failure	14 (10.9)	8 (18.6)	0.20
Liver disease	24 (18.8)	11 (25.6)	0.38
Hypothyroidism	19 (14.8)	10 (23.3)	0.24
Malignancy	89 (69.5)	30 (69.8)	1.00
Previous hyponatremia	0 (0.0)	4 (9.3)	0.004
Adrenal insufficiency	2 (1.6)	0 (0.0)	1.00
Medication use, *n* (%)			
Diuretics	29 (22.7)	18 (41.9)	0.02
Antiepileptics	47 (36.7)	8 (18.6)	0.04
Angiotensin-converting enzyme inhibitors	3 (2.3)	2 (4.7)	0.60
Beta blockers	19 (14.8)	9 (20.9)	0.35
Proton pump inhibitors	75 (58.6)	33 (76.7)	0.04
Non-steroidal anti-inflammatory drugs	53 (41.4)	33 (76.7)	< 0.001
Anticancer agents	32 (25.0)	6 (14.0)	0.14
Laxatives	36 (28.1)	23 (53.5)	0.003
Laboratory parameter, mean ± SD			
Baseline serum sodium level (mmol/L)	140.1 ± 3.3	139.1 ± 4.0	0.10

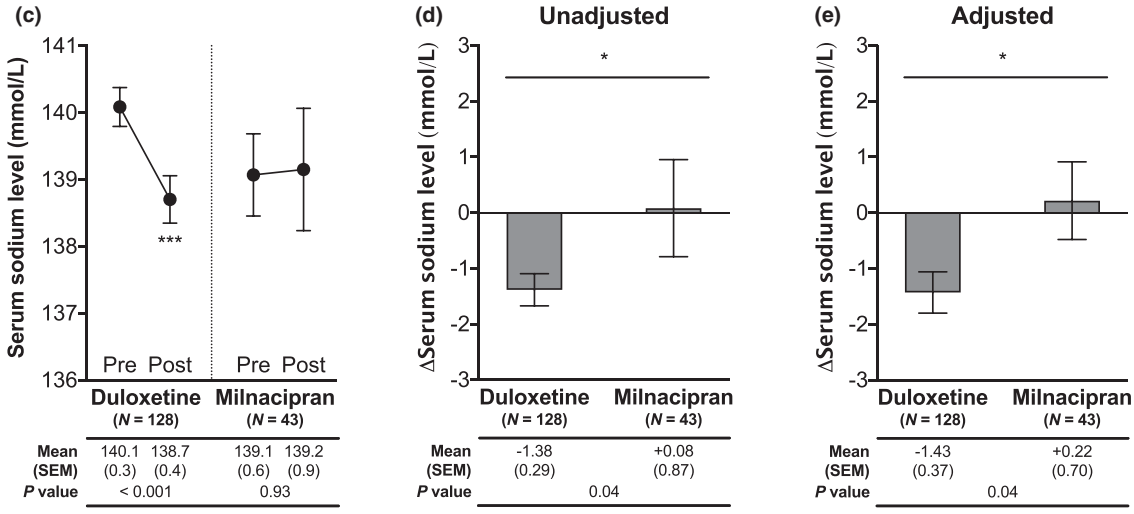


Figure 3 Within-class comparison of the effect of serotonin-noradrenaline reuptake inhibitors on serum sodium levels. (**a**) Study design. †Venlafaxine (*N* = 0) was not included. (**b**) Baseline characteristics. (**c**) Serum sodium levels before and after treatment. (**d**) Change in serum sodium levels during treatment. (**e**) Change in serum sodium levels adjusted for age, sex, medical history, medication use, and baseline serum sodium levels. Data are expressed as mean ± SEM. *$P < 0.05$, ***$P < 0.001$. SNRI, serotonin-noradrenaline reuptake inhibitor.

Pharmacoepidemiological–pharmacodynamic analysis

Finally, we performed a PE–PD analysis to explore the molecular mechanisms underlying the pharmacoepidemiological results of this study (**Figure 5**). The decrease in serum sodium levels by new-generation antidepressants was significantly correlated with their binding affinity for SERT ($r = -0.84$, $P = 0.02$; **Figure 5a**). On the other hand, no significant correlation was observed for other target molecules (**Figure 5b**). The correlation for SERT remained statistically significant even when analyzed with all antidepressants, including older ones ($r = -0.71$, $P = 0.003$; **Figure S12**) or reporting odds ratios for hyponatremia/SIADH ($r = +0.74$, $P = 0.03$ for new-generation antidepressants; $r = +0.68$, $P = 0.003$ for all antidepressants; **Figure S13**). These results not only suggest that antidepressant-induced hyponatremia is mediated by SERT inhibition but also provide mechanistic evidence that mirtazapine, fluvoxamine, and milnacipran are less likely to cause hyponatremia because of their lower binding affinity for SERT.

DISCUSSION

To the best of our knowledge, this is the first study to evaluate the effect of various antidepressants on serum sodium levels in elderly Japanese patients. This study is also the first to perform a PE–PD analysis using laboratory data from electronic medical records. This study provides the first evidence that fluvoxamine and milnacipran are less likely to cause hyponatremia.

Compared with previous studies, our triangulation study has several strengths. First, we evaluated the effect of antidepressants by objective measures (i.e., mean changes in serum sodium levels), avoiding potential bias due to the definition of hyponatremia. Second, we confirmed the effect of antidepressants through

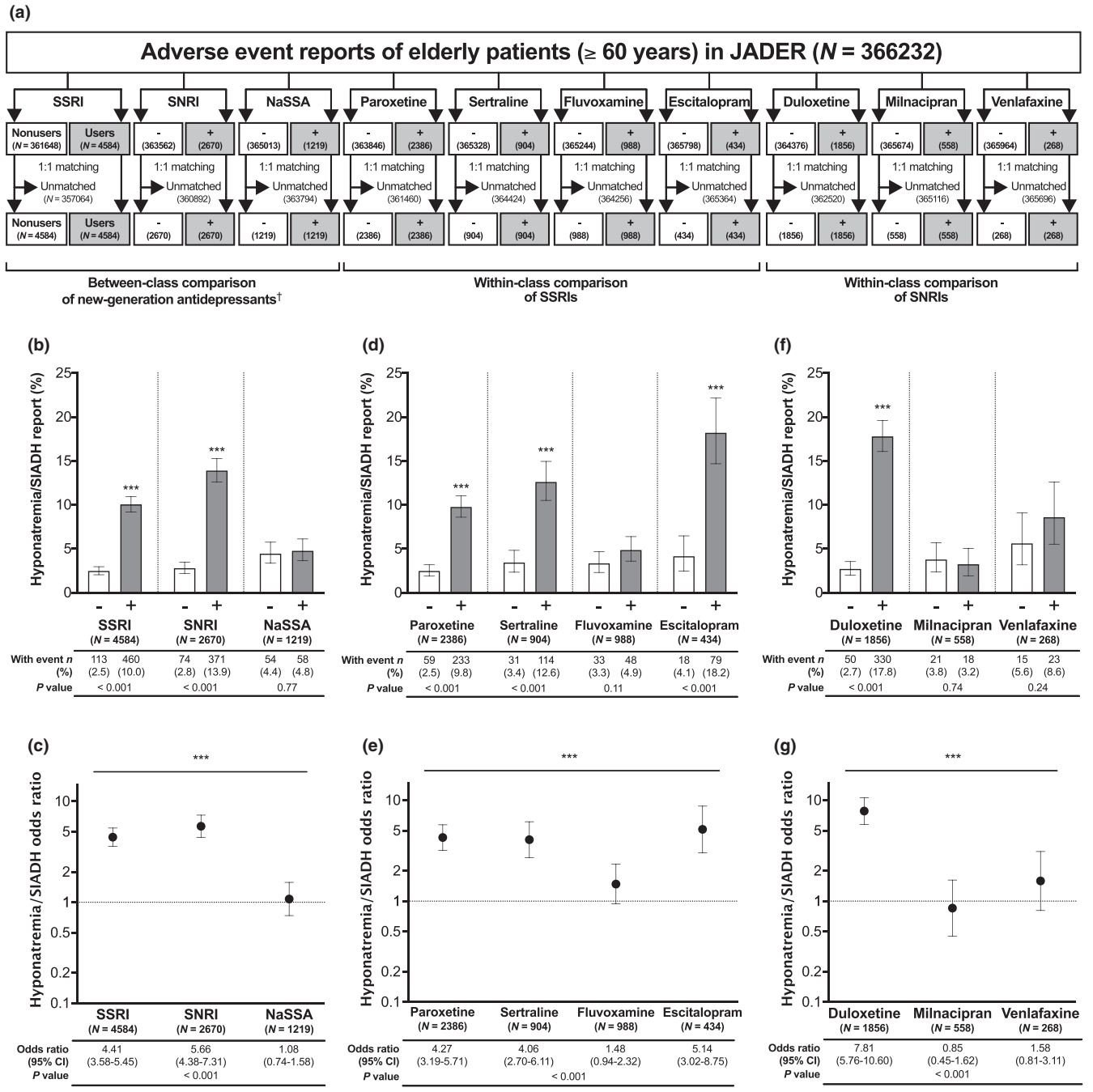
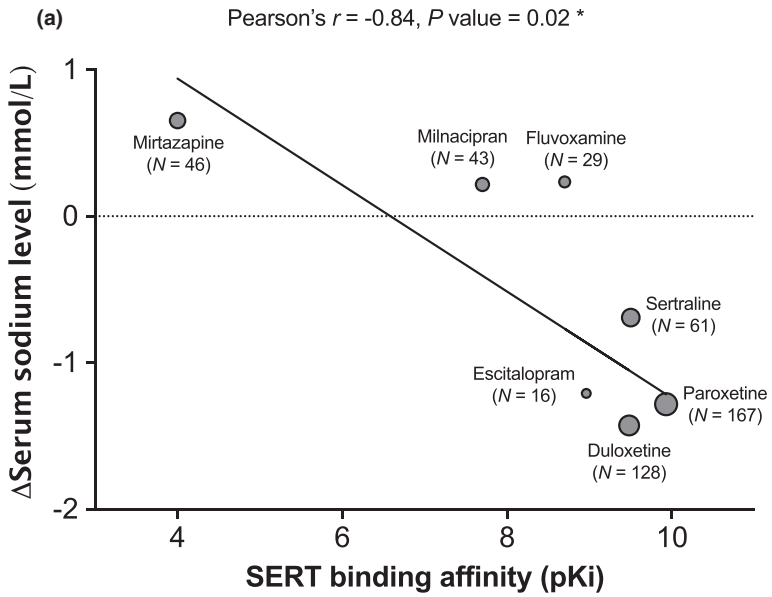


Figure 4 Relationship between new-generation antidepressants and hyponatremia/SIADH reports in JADER. (**a**) Study design. †SMS ($N = 4$) was not included because of the limited sample size. (**b**) Proportion of hyponatremia/SIADH reports with and without each class of new-generation antidepressants. (**c**) Reporting odds ratio of hyponatremia/SIADH for each class of new-generation antidepressants. (**d, e**) Within-class comparison of SSRIs. (**f, g**) Within-class comparison of SNRIs. Error bars represent 95% CI. ***$P < 0.001$. CI, confidence interval; JADER, Japanese Adverse Drug Event Report; NaSSA, noradrenergic and specific serotonergic antidepressant (mirtazapine); SIADH, syndrome of inappropriate antidiuretic hormone secretion; SMS, serotonin modulator and stimulator (vortioxetine); SNRI, serotonin-noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

multiple sources (i.e., NUSM's CDW and JADER), ensuring the accuracy and clinical relevance of our findings. Third, we explored the molecules responsible for our pharmacoepidemiological results, allowing us to support the effect of antidepressants via plausible mechanisms (i.e., differences in SERT binding affinity). For these reasons, we believe that our triangulation study provides robust evidence capable of resolving the conflicting evidence in previous studies.

Between-class comparison of new-generation antidepressants (**Figure 1**) revealed no decrease in serum sodium levels by NaSSA (mirtazapine), contrary to the significant decrease by SSRIs. This clear difference agrees with recent population-based



(b)

Target	Pearson's *r*	*P* value
Transporter		
SERT	-0.84	0.02*
NET	-0.71	0.08
DAT	-0.75	0.053
Receptor		
5-HT1A	+0.71	0.11
5-HT2A	+0.48	0.34
5-HT2C	+0.49	0.32
α_1	+0.59	0.22
α_2	+0.78	0.07
D2	+0.57	0.43
H1	+0.55	0.26
M1	-0.69	0.20
M2	-0.83	0.17
M3	-0.46	0.54
M4	-0.49	0.51
M5	-0.57	0.43

Figure 5 Correlation between changes in serum sodium levels and binding affinities to various target molecules. (**a**) Linear regression plot between adjusted mean changes in serum sodium levels (data from **Figures 1–3**) and SERT binding affinity (pKi). (**b**) Summary of regression for each target molecule. *P < 0.05. 5-HT, 5-hydroxytryptamine (serotonin); α, adrenergic; D, dopamine; H, histamine; M, muscarinic; DAT, dopamine transporter; NET, norepinephrine transporter; SERT, serotonin transporter.

studies[6–9] and is supported by our disproportionality analysis of JADER (**Figure 4b,c**). The lack of a lowering effect of mirtazapine on serum sodium levels is also supported by the minimal effect of TeCAs (**Figure S7**), as some TeCAs (e.g., mianserin) are mirtazapine analogs and can be classified as NaSSAs.[6] The decrease in serum sodium levels by TCAs (**Figure S7**) was not as pronounced as that by SSRIs, which is also consistent with many previous studies.[3,4] However, because the decrease was still significant, special attention should also be paid to patients who initiate treatment with TCAs.

Within-class comparison revealed no decrease in serum sodium levels for fluvoxamine among SSRIs (**Figure 2**) and milnacipran among SNRIs (**Figure 3**). Besides our disproportionality analysis of JADER (**Figure 4d–g**), several studies support this novel finding. In a retrospective cohort study of elderly Canadians by Gandhi *et al.*,[7] fluvoxamine was associated with a marginally lower risk of hospitalization with hyponatremia compared to citalopram (adjusted relative risk 0.47, 95% CI 0.19–1.14). In a case report by Grover *et al.*,[25] an elderly patient who had developed hyponatremia with sertraline was successfully treated with milnacipran without recurrence of hyponatremia. The heterogeneity among TCAs (**Figure S8**) is also supported by the prospective cohort study of Indian patients by Parmar *et al.*[26] that demonstrated a lower incidence of hyponatremia for imipramine (40%) than amitriptyline (48%). However, further investigation of heterogeneity among TCAs is required, as it was not confirmed in our disproportionality analysis of JADER (**Figure S11d,e**).

The precise mechanism of antidepressant-induced hyponatremia has not yet been elucidated. The generally accepted mechanism is the induction of SIADH,[3,4] and one of its clinical features (i.e., increased urine sodium levels)[27] was confirmed in **Figure S3c**. Because antidiuretic hormone is released from central vasopressin neurons whose activity is regulated by various modulators, including serotonin, noradrenaline, and dopamine,[28] it is possible that antidepressants cause hyponatremia through their actions on the central nervous system. In our PE–PD analysis (**Figure 5**), the decrease in serum sodium levels was found to be significantly correlated with the binding affinity for SERT, suggesting that antidepressant-induced hyponatremia is mediated by SERT inhibition. Although this hypothesis has already been proposed in previous studies,[3] a recent study by Mazhar *et al.*[10] presented a negative view toward this hypothesis, based on their PE–PD analysis results using the US Food and Drug Administration Adverse Event Reporting System database. However, their study did not adjust for medical history as a potential confounder, did not confirm their pharmacoepidemiological results in an independent database, and did not include some key antidepressants in their PE–PD analysis. In contrast, our study adjusted for various factors (including medical history) using rigorous statistical methods, confirmed our pharmacoepidemiological results in multiple sources, and included as many antidepressants as possible in our weighted PE–PD analysis. Therefore, contrary to the view of Mazhar *et al.*,[10] we strongly believe that SERT inhibition plays a crucial role in antidepressant-induced hyponatremia.

Our study has several limitations. First, residual confounding may exist because of the nonrandomized observational study design. Although we used rigorous statistical methods to control for confounding, unknown or unmeasured confounders may have affected our results. Second, there is some uncertainty in the results obtained in NUSM's CDW owing to the small sample size. Although we maximized the sample size by including patients regardless of their medical history, this, in turn, may have introduced confounding by indication. A larger sample size was available in JADER, but spontaneous reports suffer from other limitations,

such as under-reporting. Third, off-target mechanisms cannot be ruled out in PE–PD analysis because of the need to establish pharmacodynamic properties in advance. Because several studies suggest that antidepressants may cause hyponatremia by directly acting on the kidneys,[29–31] further research is required to elucidate the mechanism of antidepressant-induced hyponatremia.

In conclusion, our triangulation study suggests that mirtazapine, fluvoxamine, and milnacipran are less likely to cause hyponatremia because of (i) no lowering effect on serum sodium levels, (ii) no significant increase in hyponatremia reports, and (iii) lower binding affinity for SERT capable of explaining (i) and (ii). Further research is needed to confirm our findings, especially with respect to fluvoxamine and milnacipran. Our study provides clinically useful information for optimizing current antidepressant therapy as well as pharmacologically important insights for developing safer antidepressants in the future.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

T.N., T.H., and Y.T. wrote the manuscript. T.N. and S.A. designed the research. T.N. performed the research. T.N., H.A., and K.M. analyzed the data.

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