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ORIGINAL RESEARCH ARTICLE

Evaluation of hyponatremia among older adults exposed to selective serotonin reuptake inhibitors and thiazide diuretics

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Abstract

Objective: Hyponatremia is a common electrolyte disorder among older adults that can cause serious adverse effects. The purpose of this study was to assess the risk of hyponatremia with the concurrent use of selective serotonin reuptake inhibitors (SSRIs) and thiazide diuretics in an older population.

Methods: Two retrospective nested case–control studies were conducted with exposure to an SSRI or a thiazide diuretic. Persons of interest were those enrolled in Medicare and who received parts A, B, and D benefits from 2017 to 2019 and who were receiving either an SSRI or thiazide diuretic. Cases were individuals with a diagnosis of hyponatremia. Controls had no documented history of hyponatremia. A logistic regression was conducted to determine the odds of hyponatremia.

Results: Of the 551,298 patients receiving a SSRIs, the mean age was 77.8 years (Standard Deviation (*SD*) ± 8.0 years), 69% were female, and 91.23% were classified as White. We identified 701,007 individuals receiving a thiazide diuretic, with a mean age of 77.1 years (*SD* ± 7.2 years), 60.2% female, and 82.72% White. The prevalence of hyponatremia was 10.4% in patients taking thiazides alone and 9.0% in those taking SSRIs alone. On the other hand, patients on both medications had a hyponatremia prevalence of approximately 13.0%. Among SSRI users, the adjusted odds ratio (OR) of hyponatremia with concomitant use of thiazide diuretics was 1.24 (95% Confidence Interval (CI): 1.22–1.26). For thiazide users, the adjusted OR of hyponatremia with exposure to SSRIs was 1.27 (95% CI:1.24–1.29).

Conclusion: The concurrent use of thiazide diuretics and SSRIs is associated with an increased risk of hyponatremia in older populations.

KEYWORDS
drug–drug adverse effect, geriatrics, hyponatremia, SSRIs, thiazides

1 | INTRODUCTION

Hyponatremia is one of the most common electrolyte disorders in older patients.[1] Signs and symptoms of hyponatremia include headache, fatigue, confusion, convulsions, low blood pressure, muscle weakness, cramps, twitching, seizures, coma, dementia, restlessness, and agitation.[2–4] The signs and symptoms of hyponatremia typically do not appear until sodium levels fall below 130 mmol/L.[5] However, in chronic hyponatremia, 50% of patients are asymptomatic, even in those with blood serum levels less than 125 mmol/L. Recognition, prevention, and treatment of hyponatremia can be facilitated by understanding known risk factors.[5]

Decreased appetite, increased fluids, and decreased kidney function increase the risk of the development of hyponatremia. Many health conditions increase the risk of hyponatremia; however, age is the most significant risk factor.[6] In addition, older populations are taking multiple medications that may further increase the likelihood of hyponatremia. Medications from multiple drug classes have been found to increase the risk of developing hyponatremia, including antiepileptics, nonsteroidal anti-inflammatory agents (NSAIDs), angiotensin-converting enzyme inhibitors (ACEIs), antipsychotics, selective serotonin reuptake inhibitors (SSRIs), and thiazide diuretics.[7–14]

One of the major causes of hyponatremia has been identified as medications, specifically thiazides and SSRIs.[15] Selective serotonin reuptake inhibitors are thought to cause hyponatremia by inducing a syndrome of inappropriate antidiuretic hormone secretion (SIADH).[9] Thiazide diuretics deplete potassium levels and result in urinary salt loss, which may lead to hyponatremia.[16] In addition, thiazide diuretics and SSRIs are thought to reduce renal free water clearance and stimulate antidiuretic hormone (ADH).[16,17] Moreover, previous research has found a strong association between exposure to SSRIs with thiazide diuretics and hyponatremia (Odds Ratio (OR) = 11.2 for SSRIs with thiazides vs. 2.5 for thiazides alone, $p = 0.002$).[5] However, because this previous study involved fewer than 30 cases, it remains unclear if this finding is spurious. Therefore, the purpose of this study is to examine the risk of hyponatremia among a geriatric Medicare population receiving SSRIs and thiazide diuretics concomitantly.

2 | METHODS

2.1 | Data source

Medical and pharmacy claims data for adults 65 years of age or older enrolled in Medicare, comprising Medicare A, B, and D plans from January 1, 2017, to December 31, 2019, were used for this study. Medication data was obtained for individuals participating in the Medicare Part D benefit from across the United States. Data encompassed individual demographics, medical encounters with diagnosis information, a care coordination file, and pharmacy records of over 5 million enrolled beneficiaries. Demographic characteristics included age, sex, cost data, and common chronic conditions. Diagnostic information for inpatient and outpatient settings was provided in the form of the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes and Current Procedural Terminology (CPT) codes. The care coordination file contains information regarding hospitalization, such as admission date, discharge date, and length of stay. Outpatient physicians and other health care provider visits included information on diagnosis and date of service. Medication data included drug identification information, prescription fill dates, quantity dispensed, and days of supply for each prescription filled over the study period. Data used for this study were de-identified, and all files were linked using a unique patient identifier. This study was considered exempt by the University of Utah institutional review board.

2.2 | Study design and sample

A population-based nested case–control study was conducted in a cohort of older patients enrolled in Medicare from 2017 to 2019 to evaluate the risk of hyponatremia with concomitant use of SSRIs and thiazide diuretics. Persons 65 years or older with at least one prescription claim of SSRIs or thiazide diuretics were eligible for inclusion in the study. Individuals less than 65 years of age, not enrolled in or without a Medicare Part D plan during the study timeframe, those with end-stage renal disease, a history of renal transplant, or receiving loop diuretics were excluded. Follow-up began on the date of the first medication prescription, and all beneficiaries were followed until the development of hyponatremia, death, or the end of the study period, whichever occurred first.

2.3 | Cases and control definitions

Study cases were identified as individuals who had a diagnosis of hyponatremia (ICD-10 E87) after entering the study cohort. The date of the first case event served as the definition of the event date for the cases. The cases were determined at any time between the study entry date (January 1, 2017) and the study end date (December 31, 2019). Our pool of potential controls consisted of individuals who were still at risk on the date of hyponatremia occurrence for the corresponding case and who were receiving either an SSRI or a thiazide diuretic.

2.4 | Exposure and outcomes definitions

Two cohorts were studied. The first comprised patients taking SSRIs, including paroxetine, citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline, and vortioxetine, who then added a thiazide diuretic. At the same time, the second cohort consisted of patients taking thiazide diuretics who then added SSRIs to their medications. The primary outcome measure of our study was a recorded

diagnosis (from inpatient or outpatient encounters) of hyponatremia. The hyponatremia diagnosis was identified in the dataset using the corresponding ICD-10 code. To avoid double counting, only the first diagnosis of hyponatremia was used in the analysis. Furthermore, to be considered an interaction, an overlap in the use of the medications was required.

2.5 | Covariates

Potential confounders were defined as medications and medical conditions previously linked to the risk of hyponatremia. Sociodemographic characteristics such as patients' age at cohort entry, gender (male/female), and race (White, Black, and others) were included as covariates in the analysis. Additionally, clinical characteristics were accounted for using the Charlson Comorbidity Index (CCI) based on encounter diagnosis codes.[18] The use of other medications such as (ACEIs), alkylating agents, angiotensin receptor blockers (ARBs), NSAIDs, and antiepileptic medications within the study timeframe was included as a risk factor for hyponatremia.

2.6 | Propensity score matching

To ensure the robustness of our results, we also created cohorts using a one-to-one greedy propensity score matching. Controls were matched to cases based on the covariates age, sex, CCI, and other medication use from the same source population, and the same index date was assigned to the corresponding case. Accounting for all medication use is challenging due to the complexity and variability in the medication profiles of older adults. To reduce the number of categories included in the logistic regression, we used therapeutic categories of medications associated with hyponatremia risk rather than individual drugs. A propensity score analysis was conducted using a logistic regression model to generate propensity scores based on the previously mentioned covariates. A standardized mean difference (SMD) of less than 0.05 was used to assess the similarity between the matched groups. A 1:1 matching approach was conducted for cases and controls.

2.7 | Statistical analysis

We first conducted a descriptive analysis to summarize the sociodemographic characteristics of the study cohort. Pearson's chi-square test was used for categorical variables, and parametric Student's t-test was used for continuous variables to assess the baseline heterogeneity between the two cohorts. Subsequently, using bivariate analysis, we evaluated subgroup differences stratified by SSRI and thiazide concomitant use or SSRI use alone, and thiazide and SSRI concomitant use or thiazide use alone. Cohorts created via propensity score methods were also evaluated similarly.

We conducted multivariate logistic regression analyses to explore potential associations between different SSRIs and the risk of developing hyponatremia by therapeutic class. Patients concomitantly using thiazides and SSRIs were compared to those taking SSRIs only. Similarly, those taking SSRIs and thiazides were compared to those taking thiazides only. In an attempt to isolate the effect of the interaction, we conducted a subgroup analysis for those individuals who were not receiving any of the medications that were known to be associated with hyponatremia. Additional analyses were conducted to examine the risk of hyponatremia with individual SSRI medications. Furthermore, our analysis explored the relationship between the number of SSRIs taken by each patient and the risk of hyponatremia. All data analysis was conducted using SAS version 9.4 (SAS Institute, Inc).

3 | RESULTS

The SSRI cohort comprised 551,298 individuals, while the thiazides cohort comprised 701,007 individuals. The demographics of both cohorts are shown in Table 1. Given the large sample size, the differences in demographics between cases and controls were statistically significant, although they may not be clinically meaningful. Generally, the cohorts were predominantly female and of White race.

The prevalence of hyponatremia was 10.4% in patients taking thiazides alone and 9.0% in those taking SSRIs alone. Conversely, patients on both medications had a hyponatremia prevalence of 13.0%. Among those taking an SSRI, 88.5% received one unique SSRI medication, 10.1% received two SSRI medications, and 1.4% received three or more SSRI medications during the study time frame. No significant difference in hyponatremia correlated with the higher number of SSRIs.

For the SSRI cohort, the unadjusted OR for a diagnosis of hyponatremia with the concurrent use of SSRI with thiazides was 1.28 (95% CI: 1.26–1.31) compared to individuals receiving only an SSRI. After controlling for covariates, the adjusted OR was 1.24 (95% CI: 1.22–1.26). In the thiazide cohort, the concomitant use of thiazides with SSRI had an unadjusted OR of 1.51 (95% CI: 1.46–1.54) compared to those individuals on thiazides alone. After accounting for covariates, the adjusted OR for hyponatremia was 1.27 (95% CI: 1.24–1.29) (Table 2).

As mentioned above, the subgroup analysis of individuals not receiving other medications except a thiazide or SSRI was conducted. The adjusted OR (accounting for age, sex, race, CCI) for hyponatremia was 1.34 (95% CI: 1.27–1.41) for persons on SSRIs first and then receiving a thiazide diuretic. For those individuals on a thiazide first, the adjusted OR was 1.17 (95% CI 1.11–1.24) for those taking both thiazides and SSRIs (Tables S1 and S2).

To address the concerns about confounding by indication, we conducted a propensity score matching and created new cohorts for both SSRIs and thiazides. Table S3 provides the standardized mean

TABLE 1 Baseline characteristics of patients from both cohorts.

Characteristics	SSRI Cohort (*N* = 551,298)			Thiazide Cohort (*N* = 701,007)		
	SSRI only (*N* = 400,170)	SSRI + Thiazide (*N* = 151,128)	*p*-value	Thiazide only (*N* = 549,879)	Thiazide + SSRI (*N* = 151,128)	*p*-value
Age, years (mean +/− *SD*)	77.8 (±8.0)	77.0 (±7.3)	<0.001	77.1 ± 7.2	77.0 ± 7.3	<0.001
Female (%)	276,158 (69.0)	112,311 (74.3)	<0.001	331,228 (60.2)	112,311 (74.3)	<0.001
White (%)	365,077 (91.23)	135,024 (89.3)	<0.001	454,865 (82.72)	135,024 (89.3)	<0.001
CCI (mean +/− *SD*)	1.17 (1.6)	1.15 (1.56)	<0.001	0.8950 (1.39)	1.15 (1.56)	<0.001
ACEI (%)	117,942 (29.47)	61,381 (40.62)	<0.001	232,128 (42.21)	61,381 (40.62)	<0.001
ARB (%)	76,065 (19.01)	62,774 (41.54)	<0.001	219,093 (39.84)	62,774 (41.54)	<0.001
NSAID (%)	36,276 (9.07)	17,207 (11.39)	<0.001	52,284 (9.51)	17,207 (11.39)	<0.001
Alkylating Agent (%)	386 (0.10)	142 (0.09)	0.79	503 (0.09)	142 (0.09)	0.78
Antiepileptic (%)	132,342 (33.07)	50,325 (33.3)	0.11	116,662 (21.22)	50,325 (33.3)	<0.001

Abbreviations: ACEI, Angiotensin Converting Enzyme Inhibitor; ARB, Angiotensin Receptors Blocker; CCI, Charlson Comorbidity Index; NSAID, Non-Steroidal Anti-Inflammatory Drug; SD, Standard Deviation; SSRI, Selective Serotonin Reuptake inhibitor.

TABLE 2 Logistic regression for risk of hyponatremia.

	Hyponatremia (*N* = 69,005)					
	SSRI Cohort (*N* = 551,298)			Thiazide Cohort (*N* = 701,007)		
Unadjusted	Parameter	Odds ratio	95% CI	Parameter	Odds ratio	95% CI
	Thiazides	1.28	1.26–1.31	SSRI	1.51	1.46–1.54
Adjusted	Parameter	Odds ratio	95% CI	Parameter	Odds ratio	95% CI
	Thiazides	1.24	1.22–1.26	SSRI	1.27	1.24–1.29
	Age	1.025	1.024–1.026	Age	1.044	1.043–1.046
	Sex (Female)	1.047	1.027–1.067	Sex (Female)	1.212	1.19–1.233
	Race (multi-racial[a] is reference)	0.994	0.996–1.024	Race (multi-racial[a] is reference)	1.24	1.213–1.273
	ACEI	1.292	1.26–1.316	ACEI	1.215	1.193–1.238
	ARB	1.253	1.227–1.278	ARBs	1.165	1.144–1.187
	NSAID	0.950	0.922–0.979	NSAID	0.998	0.971–1.025
	Alkylating Agent	2.011	1.623–2.491	Alkylating Agent	2.075	1.706–2.523
	Antiepileptic	1.436	1.411–1.462	Antiepileptic	1.558	1.530–1.585
	CCI	1.265	1.260–1.271	CCI	1.284	1.278–1.29

Abbreviations: ACEI, Angiotensin Converting Enzyme Inhibitor; ARB, Angiotensin Receptors Blocker; CCI, Charlson Comorbidity Index; CI, Confidence Interval; NSAID, Non-Steroidal Anti-Inflammatory Drug; SSRI, Selective Serotonin Reuptake inhibitor.

[a]Multiracial include Black, Asian, North American Native, Hispanic, and other.

differences in covariates for the matched cohorts. The propensity score findings align with the primary analysis, with those receiving both medications relative to only one medication having an OR of 1.21 (95% CI: 1.18–1.23) for the SSRI cohort and 1.24 (95% CI: 1.21–1.27) for the thiazide cohort (Table 3).

To explore the relationship between individual SSRIs and the risk of hyponatremia, we conducted analyses using specific SSRIs as unique covariates. The distribution of SSRIs across the entire sample is shown in Tables S4 and S5 contains the distribution of SSRIs among those individuals with a thiazide diuretic and an SSRI. In this analysis, there were no differences observed in the risk of hyponatremia for specific SSRI medications (Tables S6 and S7).

4 | DISCUSSION

In this large retrospective nested case–control study, we assessed the risk of hyponatremia associated with concomitant use of SSRIs and thiazide diuretics among Medicare beneficiaries aged 65 years or older. Among SSRI users, the adjusted odds of hyponatremia with concomitant use of thiazide diuretics were 1.24 (95% CI: 1.22–1.26). For thiazide users, the adjusted odds of hyponatremia with exposure to SSRIs were 1.27 (95% CI:1.24–1.29) These findings suggest that monitoring of serum sodium levels and symptoms of hyponatremia may be appropriate when prescribing thiazide diuretics and SSRIs concurrently to older adults.

TABLE 3 Propensity scores matching results for both cohorts.

SSRI Cohort after matching (*N* = 289,720)			Thiazide cohort after matching (*N* = 289,722)		
Parameter	Odds ratio	95% CI	Parameter	Odds ratio	95% CI
Thiazide	1.205	1.18–1.23	SSRI	1.237	1.21–1.27

Abbreviations: CI, Confidence Interval; SSRI, Selective Serotonin Reuptake Inhibitors.

TABLE 4 Risk factors for hyponatremia.

Type	Comments
Age/Gender/BMI	65 years of age or older[6,14]; female gender,[32,33] low body mass index (BMI)[34]
Diets/Liquids	Salt restriction,[35] high free water intake,[35] decreased appetite[6]
Comorbidities	Low serum sodium, congestive heart failure,[14] cirrhosis,[14] pneumonia,[14] hyperglycemia,[36] hypothyroidism,[37] acquired immunodeficiency syndrome,[38] decreased kidney function[6]
Other Drugs[7-14]	Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, antiepileptics, amiodarone, antipsychotics, anticancer, and non-steroidal anti-inflammatory drugs.
Genomics	The a396t variant of slco2a1 may increase risk of thiazide-mediated hyponatremia[39]

Among individuals who use SSRIs and thiazide diuretics concurrently, hyponatremia is thought to be caused by the SIADH.[19–21] This is where ADH is released in excess quantities, causing the body to reabsorb water in greater quantities than needed.[2,19,22] This excess water dilutes the serum sodium but does not impair the kidneys' ability to excrete sodium from the body. These two mechanisms can increase the risk of hyponatremia in older individuals.[19]

The results of our study are consistent with previous literature concerning hyponatremia and exposure to SSRIs with thiazide diuretics. In the Netherlands in 2002, a study conducted to assess the association of SSRIs and hyponatremia. They found that the concurrent use of SSRIs and diuretics had a synergistic effect on hyponatremia when compared with the nonuse of diuretics (OR 8.4; 95% CI 2.1, 34), and this effect was more common in patients aged 65 years or older (OR 13.5; 95% CI 1.8, 101).[5] However, their study population was small, comprising 29 cases and 78 controls. They were also unable to confirm that diuretics alone are associated with hyponatremia, whereas studies with larger population sizes were able to detect diuretics as a risk factor for hyponatremia.[23,24]

Our research suggests that despite the known risk associated with the concomitant use of SSRIs and thiazide diuretics, the occurrence of hyponatremia remains common. Over 10% of Medicare beneficiaries exposed to both medications had a diagnosis of hyponatremia. The use of these agents is common as well. We found that individuals were often exposed to both agents, with 27% in the SSRI cohort and 22% in the thiazide cohort on concomitant therapy. With this issue persisting in approximately one-fourth to one-third of our Medicare beneficiary population, there is a high likelihood that many patients with hyponatremia may be underdiagnosed. Signs and symptoms of severe hyponatremia may present as convulsions, confusion, restlessness, or agitation, which may be misdiagnosed as seizures, dementia, or mood disorders. This could lead to unnecessary prescription medications and increase the cost of care with unnecessary treatments.[25,26]

Few studies have assessed the association between hyponatremia and the concomitant use of SSRIs and thiazide diuretics; however, many have demonstrated a strong association between SSRIs alone and the occurrence of hyponatremia. In Denmark, researchers found an increased risk for hyponatremia, with the risk being the highest within the first 2 weeks of starting SSRI therapy (incidence rate ratio (IRR) 8.72: 95% CI 7.97–9.54)[27]; with the incidence of hyponatremia increasing with age. Another study conducted in Canada assessed the use of second-generation antidepressants (SSRI and SNRI)in older adults and found an approximately 5-fold increase in the 30 days risk for hospitalization with hyponatremia when compared to no antidepressants (relative risk (RR), 5.46; 95% CI, 4.32–6.91).[24] A study completed in Bengal found that the incidence of hyponatremia varied by age in patients taking an SSRI, with older individuals more likely to experience hyponatremia.[23] The studies discussed above did not evaluate the concurrent use of SSRIs with thiazide diuretics. Our study, with a large sample size of older adults, with over 500,000 patients, fills this gap in research.

Our study found that the increase in odds of hyponatremia is (24% and 27%) higher among those exposed to both SSRIs and thiazide diuretics as compared to either agent alone. This finding is not new as case reports exist in the literature.[7,20,28–30] In 2004, a case report described two older patients who experienced hyponatremia, one (84 years of age) with a serum sodium level of 122 mmol/L and the other (63 years of age) having a serum sodium of 109 mmol/L. Both patients presented to the emergency room with lethargy, confusion, and headache.[20] Both had recently started fluoxetine and hydrochlorothiazide within the previous 2 weeks. Case reports of hyponatremia due to SSRIs alone also exist. In a report from 1996, two cases of hyponatremia were discussed, with both being women in their 70s. One patient had begun fluoxetine 20 mg daily 6 weeks before hospitalization with drowsiness and weakness. Her serum sodium was 103 mmol/L.[28] The other patient was admitted to the

hospital 5 days after beginning 20 mg daily of fluoxetine with a serum sodium of 110 mmol/L. A separate case–control study found that diuretics and fluoxetine were the two medications associated with the highest risks of hyponatremia (OR = 8.2 and OR = 21.4, respectively).[30]

Due to the association between hyponatremia and the concurrent use of SSRIs and thiazide diuretics, we recommend that if concurrent therapy is deemed necessary, the patient should be monitored for evidence of hyponatremia and should be advised of symptoms to look for. Using other classes of antidepressants may be an option, depending on the indication, as some antidepressants have been found to have a lower risk of hyponatremia (e.g., mirtazapine, bupropion) and may be considered an appropriate alternative to SSRIs.[3,31] Based on our findings, we recommend monitoring serum sodium levels in patients 65 years and older who are concurrently using an SSRI and thiazide diuretic. In addition to SSRIs and thiazide diuretics, there are several other risk factors that may result in hyponatremia. These factors, including age, sex, underlying comorbidities, and other concurrent medication, are critical in determining an individual's susceptibility to developing hyponatremia. Table 4 provides a summary of known risk factors for hyponatremia.

There are several limitations to this study. We were not able to exclude all comorbid conditions that can cause hyponatremia. Because thiazide diuretics are commonly prescribed to treat heart failure, we deemed it necessary to include these patients in our results. We could not assess serum values for sodium due to the lack of laboratory results. As a result, we had to rely on the diagnosis of hyponatremia, which may under-report the true incidence. Furthermore, because medical coders are not clinicians and we utilized ICD-10 codes for data analysis, diagnoses may be miscoded. Coding also involves a degree of subjectivity, potentially leading to instances where encounter claims did not have a hyponatremia diagnosis despite having the condition as witnessed by a clinician. Additionally, our study lacked information on the dose of thiazides and SSRIs, which limited our ability to evaluate a potential dose–response relationship. On the other hand, the relatively short timeframe of our study makes it challenging to distinguish between short-term and long-term therapy, further limiting our ability to assess the duration of treatment as a factor influencing the risk of hyponatremia. Although we focused on medications strongly associated with hyponatremia, not all medications that may be associated with hyponatremia were accounted for. The decision to prioritize medications with evidence of association was to help ensure a focused analysis. However, this still represents a limitation, as other less frequently associated or emerging medications may also contribute to hyponatremia.

Moreover, we could not evaluate medication adherence. The analysis used prescription claims to indicate exposure, but it is possible that individuals were not taking the medications as prescribed. Additionally, our analysis could not incorporate daily sodium intake as confounding factors for hyponatremia because we could not assess patients' dietary intake. Furthermore, we did not have a method to determine if patients were taking over-the-counter NSAIDs, which may also affect sodium levels. Patients may experience severe diarrhea and/or vomiting independent of SSRI/thiazide use, leading to a subsequent diagnosis of hyponatremia that was not directly related to the products under investigation. This remains a limitation of this study. However, there is a likely under-reporting of cases of hyponatremia because we relied only on a medical claim to have a diagnosis of the condition. This approach could contribute to the discrepancy between our findings (lower rates) and those reported previously.

Although there are limitations to this study, our large sample of over 500,000 Medicare beneficiaries allowed us to estimate the risk of hyponatremia diagnosis with the concomitant use of SSRIs and thiazide diuretics. Additionally, we used a one-to-one greedy propensity score matching to control for potential confounding and validate the overall results. We assessed concomitant medications and adjusted our findings based on the increased risk for hyponatremia associated with each one.

In conclusion, prescribing SSRIs in combination with thiazide diuretics to older populations should be approached with caution due to the increased risk of hyponatremia. Careful assessment of individual patient risk factors and close monitoring of electrolyte levels are recommended when it is necessary for these medications to be used together. This approach allows for balancing the benefits of therapy with the potential risks, ensuring patient safety through proactive management.

AUTHOR CONTRIBUTIONS

All authors have read and approved the final version of the manuscript for submission. TM, PH, and DCM were pivotal in the conception and design of the study. The acquisition, analysis, and interpretation of data were collaboratively undertaken by all authors, highlighting the team's comprehensive involvement in the research process. The initial draft of the manuscript was prepared by TM, AT, and KB, demonstrating their significant role in synthesizing the research findings into a coherent document. Critical revisions for important intellectual content were contributed by all authors, ensuring the manuscript's integrity and depth. Statistical analyses were expertly handled by AT, KB, and DCM, underscoring their analytical expertise. DCM also took on the role of study supervision, guiding the project to its fruition.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Centers for Medicare and Medicaid Services. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the author(s) with the permission of Centers for Medicare and Medicaid Services.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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