Major depression is a common psychiatric disorder in older adults, affecting 10% to 20% of medically hospitalized elderly patients. It is reported that 10% to 34.5% of older persons living in the community also experience clinically significant depressive symptoms. Major depression in older patients is managed in the primary care setting. According to a recent report on national trends in outpatient treatment, depressed patients were 4.8 times more likely to receive treatment with an antidepressant in 1997 than in 1987. The marked increase in pharmacological treatment of this disorder is due in part to the introduction of a new class of highly effective antidepressant drugs known as the selective serotonin reuptake inhibitors (SSRIs). Owing to the relatively benign adverse effect profile of SSRIs, these agents are often prescribed as the first-line treatment of depression in older adults. Although these agents are reportedly safer than the tricyclic antidepressants, they are not without risk or adverse effects.

Since the introduction of SSRIs more than a decade ago, the medical literature is replete with isolated case reports of clinically significant hyponatremia in aged patients treated with these agents. In a case note review, Strachan and Shepherd reported hyponatremia in 5 (28%) of 18 elderly patients prescribed fluoxetine hydrochloride and 8 (22%) of 37 prescribed paroxetine, although an earlier retrospective case-control study of 845 patients documented that hyponatremia developed in 1 of 200 patients treated per year with these agents. More recently, Kirby et al recently reported a 39% incidence of hyponatremia in a retrospective analysis of 74 elderly inpatients who were receiving treatment with an SSRI or with venlafaxine hydrochloride. Despite the growing number of case and retrospective reports of SSRI-induced hyponatremia, prospective evaluation of the safety of these agents is lacking in individuals older than 65 years, the fastest growing segment of our population. Although severe hyponatremia can be fatal, symptoms associated with mild to moderate hyponatremia are nonspecific (eg,
nation.18 Medical burden was quantified by the Cumulative Illness Rating Scale–Geriatrics.19 Adrenal, renal, and thyroid functions were obtained, and laboratory measures were assessed in all patients. A complete medical, psychiatric, and medication history was obtained, and laboratory measures were assessed in all patients at the baseline visit. Patients underwent screening before entry into the study. All patients had a score of 15 or greater on the 17-item Hamilton Rating Scale for Depression17 and a score of 18 or higher on the Folstein Mini-Mental State Examination.16 Medical burden was quantified by the Cumulative Illness Rating Scale–Geriatrics.16 Adrenal, renal, and thyroid function were determined to be normal, and glucose levels were within physiologic limits (60-110 mg/dL [3.3-6.0 mmol/L]). None of the patients in whom hyponatremia developed had concurrent medical conditions or were prescribed other medications known to cause hyponatremia.

Plasma concentrations of sodium were determined before initiating paroxetine therapy and after 1, 2, 4, 6, and 12 weeks of treatment. In one patient, development of symptoms of hyponatremia within 24 hours of initiating paroxetine therapy necessitated the immediate measurement of the plasma sodium level. Patients with sodium levels near the lower limit of the physiologic range before initiation of paroxetine therapy were instructed to restrict daily fluid intake in an attempt to minimize risk for development of hyponatremia. In a subset of individuals, blood samples were collected for the purpose of measuring levels of ADH, glucose, serum urea nitrogen (SUN), and creatinine to investigate the potential etiology of hyponatremia in these patients.

Patients whose plasma sodium level was less than 135 mEq/L at any assessment returned to the clinic to undergo additional laboratory tests, including measurement of plasma sodium, ADH, glucose, SUN, and creatinine levels. A spot urine sample was also collected for the measurement of the urine sodium level and osmolality in these individuals. We notified the patient’s primary care physician of the development of hyponatremia and discussed a suggested plan for management.

Plasma paroxetine concentrations were measured to assess compliance and to determine whether the concentration of paroxetine was a factor in the development of hyponatremia. All reported symptoms (eg, confusion, anorexia, or fatigue) or adverse events (eg, abrupt changes in mental status or incidence of falls) were documented at each visit and evaluated at weekly clinical research meetings as part of a National Institutes of Health–mandated data, safety, and monitoring plan.

LABORATORY ANALYSIS

Laboratory measures, including levels of sodium, glucose, SUN, and creatinine, were performed by the Clinical Chemistry Laboratory at the University of Pittsburgh Medical Center using an automated system (Vitros 950 Clinical Chemistry System; Ortho-Clinical Diagnostics, Inc, Rochester, NY). The within-laboratory coefficients of variation were 0.9% for plasma sodium level, 1.6% for urine sodium level, 1.6% for SUN level, 1.1% for creatinine level, and 1.0% for glucose level. Plasma osmolality was calculated using the following formula:

\[
\text{Plasma Osmolality} = 2(\text{Sodium}) + (\text{Glucose} \div 20) + (\text{SUN} \div 3)
\]

Urine osmolality was determined by means of freezing point depression with a within-laboratory coefficient of variation of 1.4%.

Plasma ADH levels were determined by radioimmunoassay methods. Blood samples were obtained by direct venipuncture into a 10-mL venous blood collection tube (Vacutainer; Becton, Dickinson and Co, Franklin Lakes, NJ) containing 143 US Pharmacopeia units of heparin sodium. Blood was centrifuged at 4°C at 1500g for 10 minutes. The plasma was separated, transferred into polypropylene storage tubes, and frozen at −80°C until analyzed. The radioimmunoassay system used for determining ADH levels was based on methods previously described by Robertson and colleagues21 and subsequently modified.22,23 The intra-assay and interassay coefficients of variation range from 9% to 7% at each concentration of the standard curve (0.5-20 pg/mL [0.5-18.5 pmol/L]).

Plasma paroxetine levels were determined using reverse-phase high-performance liquid chromatography and UV detection.24 Blood samples were collected by venipuncture into a 10-mL venous blood collection tube containing 13% menadione EDTA. Blood was centrifuged at 4°C at 1500g for 10 minutes. The plasma was separated, transferred into polypropylene storage tubes, and frozen at −80°C until analyzed. The high-performance liquid chromatography column used for separation was an Ultrasphere 5µ C18, 150 ¥ 2.0-mm internal diameter (Phenomenex Inc, Torrance, Calif). The mobile phase consisted of potassium phosphate and acetonitrile (62:38, vol/vol), with a pH of 2.4. The wavelength used for UV detection was 205 nm, and the assay was linear, from 5 to 500 ng/mL. Interassay variation for this assay was 1.4% for 250 ng/mL and 3.2% for 75 ng/mL. Commercially purchased analytical paroxetine controls were analyzed in every assay.

METHODS

This study was approved by the Institutional Review Board of the University of Pittsburgh, Pittsburgh, Pa, and was ancillary to an ongoing Institutional Review Board–approved antidepressant treatment protocol in which the US Food and Drug Administration–approved SSRI paroxetine was prescribed. All patients were instructed to restrict daily fluid intake in an attempt to minimize risk for development of hyponatremia. In a subset of individuals, blood samples were collected for the purpose of measuring levels of ADH, glucose, serum urea nitrogen (SUN), and creatinine to investigate the potential etiology of hyponatremia in these patients.
Hyponatremic Patients

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STATISTICAL ANALYSIS

Descriptive statistics were used to summarize demographic, clinical, and baseline laboratory variables. All data are expressed as mean ± SD.

At the completion of the study, patients were classified into 1 of the following 2 groups: patients with hyponatremia (sodium level, <135 mEq/L on ≥1 occasions) or those who maintained normonatremia (sodium level, ≥135 mEq/L throughout the study). Univariate logistic regressions were performed to examine between-group differences in baseline demographic, clinical, and laboratory measures. We then performed a multivariate logistic regression using sex, medical burden, and all variables identified in the univariate logistic regression analyses that were significant at \(P<.10\). The final model was obtained by a backward stepwise regression procedure (threshold removal set at \(P<.10\)).

Maximum change in plasma sodium concentration after initiation of paroxetine therapy was plotted according to baseline sodium concentration in all subjects. A receiver operating characteristics curve was calculated to show the sensitivity and specificity of determining a cutoff for baseline plasma sodium as a reliable screening measure to identify patients at risk for development of hyponatremia.

Plasma osmolality and ADH levels measured on the date closest to the initiation of paroxetine treatment were chosen for graphic presentation and correlation analyses. Plasma paroxetine and ADH levels were plotted and correlation analyses were performed to determine whether any relationship existed between them. Statistical analyses were performed using SAS software, version 8.2.25

RESULTS

Baseline demographic, clinical, and laboratory data for the 75 patients are displayed in Table 1. Hyponatremia developed in 9 (12%) of the 75 patients after initiation of paroxetine treatment and constitute the hyponatremic group, whereas 66 individuals constitute the normonatremic group. Mean time to development of hyponatremia after starting paroxetine therapy was 9.3±4.7 days (median, 9 days; range, 1-14 days; \(n=8\)). One subject started the study while receiving paroxetine and, consequently, the time to onset of hyponatremia was not determined. The mean dose of paroxetine at the time of hyponatremia was 12.5±1.6 mg, with hyponatremia developing in 8 of the 9 patients while prescribed 10 mg of paroxetine. There were no correlations between plasma paroxetine concentrations and measures of plasma sodium or plasma ADH levels (data not shown).

Maximum change in sodium concentration from baseline is displayed in Figure 1 for all patients relative to their baseline sodium concentration. Although sodium concentrations decreased in most patients after initiation of paroxetine therapy, the greatest declines were observed in the 9 patients who met criteria for hyponatremia. Eight patients had at least an 8-point drop in sodium concentration, and 6 had more than 1 sodium level below the cutoff of 135 mEq/L. Most patients in whom

Table 1. Baseline Demographic, Clinical, and Laboratory Data for Normonatremic and Hyponatremic Patients

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Findings*</th>
<th>Median</th>
<th>No. of Patients</th>
<th>Findings*</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>66</td>
<td>75.2±6.1 (63.0-90.0)</td>
<td>74.5</td>
<td>9</td>
<td>75.8±6.2 (68.0-84.0)</td>
</tr>
<tr>
<td>No. (%) male</td>
<td>66</td>
<td>21 (32)</td>
<td>NA</td>
<td>9</td>
<td>1 (11)</td>
</tr>
<tr>
<td>No. (%) white</td>
<td>66</td>
<td>59 (89)</td>
<td>NA</td>
<td>9</td>
<td>9 (100)</td>
</tr>
<tr>
<td>BMI</td>
<td>66</td>
<td>28.2±6.9 (16.8-56.5)</td>
<td>28.3</td>
<td>9</td>
<td>22.3±3.1 (17.9-25.7)</td>
</tr>
<tr>
<td>CIRS-G score</td>
<td>66</td>
<td>9.6±3.7 (2.0-19.0)</td>
<td>10.0</td>
<td>9</td>
<td>8.2±3.1 (4.0-14.0)</td>
</tr>
<tr>
<td>17-Item Hamilton-D score</td>
<td>66</td>
<td>19.4±3.9 (8.0-30.0)</td>
<td>19.0</td>
<td>9</td>
<td>19.3±2.6 (15.0-22.0)</td>
</tr>
<tr>
<td>Folstein MMSE score</td>
<td>62</td>
<td>28.1±2.0 (23.0-30.0)</td>
<td>29.0</td>
<td>9</td>
<td>26.7±2.7 (21.0-29.0)</td>
</tr>
<tr>
<td>Sodium level, mEq/L</td>
<td>66</td>
<td>140.9±2.3 (136.0-146.0)</td>
<td>141.0</td>
<td>9</td>
<td>137.0±2.2 (135.0-142.0)</td>
</tr>
<tr>
<td>SUN, mg/dL</td>
<td>58</td>
<td>17.8±7.6 (9.0-50.0)</td>
<td>16.0</td>
<td>8</td>
<td>14.3±4.8 (7.0-20.0)</td>
</tr>
<tr>
<td>Creatinine level, mg/dL</td>
<td>59</td>
<td>1.0±0.3 (0.6-2.3)</td>
<td>1.0</td>
<td>8</td>
<td>0.9±0.1 (0.7-1.0)</td>
</tr>
<tr>
<td>ADH, pg/mL</td>
<td>42</td>
<td>2.1±0.8 (1.0-4.9)</td>
<td>1.8</td>
<td>3</td>
<td>1.7±0.5 (1.4-2.2)</td>
</tr>
<tr>
<td>Plasma osmality, mOsm/kg</td>
<td>58</td>
<td>293.3±5.5 (281.4-307.5)</td>
<td>293.1</td>
<td>9</td>
<td>282.6±4.1 (278.1-290.8)</td>
</tr>
</tbody>
</table>

Abbreviations: ADH, antidiuretic hormone; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CIRS-G, Cumulative Illness Rating Scale–Geriatrics; Hamilton-D, Hamilton Rating Scale for Depression; MMSE, Mini-Mental State Examination; NA, not applicable; SUN, serum urea nitrogen.

SI conversion factors: To convert ADH to picomoles per liter, multiply by 0.923; creatinine to micromoles per liter, multiply by 88.4; SUN to millimoles per liter, multiply by 0.357.

*Unless otherwise indicated, data are expressed as mean ± SD (range), with medians.

Figure 1. Maximum observed change from baseline sodium level compared with baseline sodium concentration for patients who became hyponatremic (n=9) and those who remained normonatremic (n=66). The dashed line represents no change from baseline sodium level. Duplicate values are represented by a single circle.
Table 2. Univariate Logistic Regression Analyses for Presence or Absence of Hyponatremia as a Function of Each Potential Risk Factor at Baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>x² Test Statistic</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.02 (0.90 to 1.14)</td>
<td>0.07</td>
<td>.80</td>
</tr>
<tr>
<td>Female</td>
<td>3.73 (0.44 to 31.81)</td>
<td>1.45</td>
<td>.23</td>
</tr>
<tr>
<td>BMI</td>
<td>0.79 (0.66 to 0.95)</td>
<td>6.60</td>
<td>.01</td>
</tr>
<tr>
<td>Total CIRS-G score</td>
<td>0.90 (0.73 to 1.10)</td>
<td>1.10</td>
<td>.29</td>
</tr>
<tr>
<td>17-Item Hamilton-D score</td>
<td>1.00 (0.82 to 1.20)</td>
<td>0.003</td>
<td>.95</td>
</tr>
<tr>
<td>Folstein MMSE score</td>
<td>0.76 (0.56 to 1.02)</td>
<td>3.40</td>
<td>.07</td>
</tr>
<tr>
<td>Sodium level</td>
<td>0.48 (0.31 to 0.73)</td>
<td>11.82</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SUN level</td>
<td>0.90 (0.77 to 1.06)</td>
<td>1.67</td>
<td>.20</td>
</tr>
<tr>
<td>Creatinine level</td>
<td>0.15 (0.003 to 7.32)</td>
<td>0.91</td>
<td>.34</td>
</tr>
<tr>
<td>Plasma osmolality</td>
<td>0.63 (0.47 to 0.84)</td>
<td>9.72</td>
<td>.002</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CI, confidence interval; CIRS-G, Cumulative Illness Rating Scale–Geriatrics; MMSE, Mini-Mental State Examination; OR, odds ratio; SUN, serum urea nitrogen.

Table 3. Multivariate Logistic Regression Analyses for Presence or Absence of Hyponatremia as a Function of Each Potential Risk Factor at Baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>x² Test Statistic</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multivariate model</td>
<td>30.30 (0.59 to &gt;.99)</td>
<td>2.87</td>
<td>.09</td>
</tr>
<tr>
<td>Sex</td>
<td>17.72 (0.92 to 340.43)</td>
<td>3.63</td>
<td>.06</td>
</tr>
<tr>
<td>BMI</td>
<td>0.74 (0.56 to 0.99)</td>
<td>4.18</td>
<td>.04</td>
</tr>
<tr>
<td>Baseline sodium level</td>
<td>0.40 (0.22 to 0.73)</td>
<td>8.83</td>
<td>.003</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CI, confidence interval; CIRS-G, Cumulative Illness Rating Scale–Geriatrics; MMSE, Mini-Mental State Examination; OR, odds ratio; SUN, serum urea nitrogen.

Figure 2. Plasma osmolality compared with plasma antidiuretic hormone (ADH) levels after initiation of paroxetine therapy for hyponatremic (n=5) and normonatremic (n=41) individuals. The ADH values were not available for all subjects. The vertical dashed line represents the osmotic threshold, whereas the horizontal dashed line represents the lower limit of detection of the ADH assay.

We identified a 12% incidence of hyponatremia that developed within 1 to 14 days after initiation of paroxetine therapy in this cohort of depressed older patients. Although female sex and lower baseline plasma sodium level were significant independent predictors of hyponatremia, the use of an SSRI, paroxetine, in elderly depressed patients.

Risk factors for the development of paroxetine-induced hyponatremia in these patients included lower baseline sodium levels and lower BMI. Although female sex was not a significant predictor of hyponatremia in
this study, it approached significance (Table 3) and has been identified in other studies as correlating with development of hyponatremia.

In general, the incidence of hyponatremia is higher among older patients, possibly due to age-related physiological changes in water and electrolyte handling; however, the extent of these physiological changes is highly variable. Examples of age-related physiological changes in water and osmotic homeostasis include a reduction in total body water level and/or diminished renal blood flow and glomerular filtration; increased ADH secretion or lack of ADH suppression in response to osmolar or pharmacological stimuli, and decreased renal response to ADH. Despite these factors, whether age is an independent risk factor is difficult to discern owing to the presence of comorbid medical conditions or concomitant prescribed medications that are known to cause hyponatremia or alter ADH secretion.

As shown in Figure 1, sodium concentrations declined in most patients in the normonatremic and hyponatremic groups after initiating paroxetine therapy. However, the development of hyponatremia does not appear to be dose related, as plasma paroxetine concentrations were not associated with risk for development of hyponatremia. A 10-mg dose of paroxetine was prescribed for 8 of the 9 patients when the episode of hyponatremia was detected. On detection, paroxetine therapy was held or discontinued, and patients were instructed to restrict daily fluid intake to 1000 mL or less until the plasma sodium level normalized (eg, sodium level, ≥135 mEq/L).

The maintenance of water homeostasis and physiological serum sodium levels is highly dependent on ADH. This nonapeptide is synthesized within the hypothalamus and transported to, stored in, and released from the posterior lobe of the pituitary gland in response to physiological stimuli. By binding to ADH receptors in the renal tubules or collecting ducts of the kidney promoting reabsorption of water, ADH exerts the major control over osmolality in the body. Antidiuresis leads to a decrease in plasma osmolality and an increase in urine osmolality.

In euvolemic, normonatremic healthy individuals, circulating levels of ADH are 1 to 2 pg/mL (0.9-1.8 pmol/L). Secretion of ADH is triggered appropriately in response to physiological stimuli such as high plasma osmolality or hypovolemia. Conversely, ADH secretion should be suppressed when plasma osmolality falls below the osmotic threshold (<280 mOsm/kg) and intravascular volume is replete. Secretion of ADH, despite low plasma sodium level or osmolality (as in the patients in whom hyponatremia developed in this study) is inappropriate and indicates the presence of a nonosmotic stimulus for ADH release. Some examples of nonosmotic stimuli of ADH secretion include ADH production of malignancies, pulmonary disorders, central nervous system disorders (eg, stroke, trauma, and infection), and certain pharmacological agents (eg, thiazide diuretics, antipsychotics, antidiuretics, and non-steroidal anti-inflammatory drugs). Experimental studies in rats suggest that serotonin is a potential stimulator of ADH secretion. The SSRIs, including paroxetine, are known to block the reuptake of serotonin in the central nervous system. Thus, inappropriate secretion or enhanced action of ADH as a result of enhanced serotonergic tone may contribute to the development of SSRI-induced hyponatremia in older patients, provided water intake is sufficient. Even if SSRIs stimulate ADH secretion, hyponatremia will not occur until patients ingest or are infused with excess fluids. A criterion for the diagnosis of the syndrome of inappropriate ADH secretion is that individuals be volume replete. Consequently, the effect of an SSRI to induce hyponatremia may not become manifest until the patient enters a phase of increased fluid ingestion. In this study, several patients in whom hyponatremia developed had temporally associated complaints of urinary tract infections and constipation, and many of these patients were encouraged to drink fluids to alleviate these conditions. Patients with normal kidney function are capable of excreting large volumes of hypotonic urine daily. However, transient periods of intense drinking may exceed the hourly capacity for free water excretion, and transient hyponatremia may develop in such instances, especially in patients prescribed psychotropic medications that enhance the release or action of ADH.

Recent improvements in detection and diagnosis of depressive disorders in the elderly along with use of SSRIs for treatment of anxiety disorders has resulted in an increased number of older patients being prescribed SSRIs. As such, a greater number of individuals are at risk for development of SSRI-induced hyponatremia. Patients with SSRI-induced hyponatremia may be asymptomatic, and therefore routine monitoring of sodium concentrations in elderly patients prescribed an SSRI is essential. Failure to detect and manage mild hyponatremia may result in progression to moderate or severe hyponatremia that can lead to seizures, coma, or death. Thus, early detection, appropriate monitoring, and treatment of hyponatremia in older patients who are prescribed an SSRI will have a significant public health impact by reduction of health care costs associated with preventable adverse medical events.

Hyponatremia is an underrecognized and potentially serious complication of paroxetine treatment in older patients. Hyponatremia associated with SSRIs has been postulated to be due to the syndrome of inappropriate ADH secretion. In this prospective study, we provide evidence in support of a mechanism mediated by the syndrome of inappropriate ADH secretion for paroxetine-induced hyponatremia in these older individuals. Plasma sodium concentrations decreased in nearly all of the older depressed patients prescribed paroxetine in this study. However, the risk for development of hyponatremia was highest in women with a low BMI who had sodium concentrations near the lower end of the physiologic range before initiating treatment. The risk for development of hyponatremia was highest in the first 2 weeks of paroxetine treatment and was not related to paroxetine concentrations. Therefore, we recommend monitoring sodium and SUN levels before initiating treatment with paroxetine or other SSRIs and at 1 and 2 weeks after initiation of treatment. This is especially important for patients who present with additional risk factors such as female sex, low BMI, and a baseline plasma sodium level of 138 mEq/L or less. At minimum, a sodium level should be measured in all elderly patients who exhibit abrupt
changes in mental status (eg, lethargy or confusion) any time during treatment with an SSRI. If hyponatraemia develops and continuation of SSRI therapy is desired, long-term restriction of daily fluid intake (eg, 800-1000 mL) has been somewhat successful, although patient compliance is often poor. Failure to respond to fluid restriction warrants discontinuation of the causative medication until sodium levels normalize.

**CONCLUSIONS**

The results obtained from this prospective study provide a foundation for understanding the etiology and risk factors associated with paroxetine-induced hyponatraemia. Development and implementation of a rational plan for prescribing and safety monitoring of SSRIs in the aged should be based on an increased understanding of this common adverse event.

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**REFERENCES**