Paroxetine-Induced Hyponatremia in Older Adults

A 12-Week Prospective Study

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Background: Older depressed patients are at high risk for development of hyponatremia after initiation of the selective serotonin reuptake inhibitor paroxetine, despite clinical monitoring and preventive management. The purposes of this study were to determine the incidence and etiology of paroxetine-induced hyponatremia in older patients and to identify patient characteristics that may account for variability in susceptibility to this adverse event.

Methods: This prospective, longitudinal study was conducted in a university-based ambulatory psychiatric research clinic from August 1999 through September 2001. Patients included 75 men and women aged 63 through 90 years (mean±SD age, 75.3±6.0 years) who received a diagnosis of a current Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, major depressive episode and were prescribed paroxetine. We monitored plasma sodium levels before initiating paroxetine therapy and after 1, 2, 4, 6, and 12 weeks of treatment. In a subset of individuals, we measured levels of antidiuretic hormone, glucose, serum urea nitrogen, and creatinine. Hyponatremia was defined as a plasma sodium level of less than 135 mEq/L after initiation of paroxetine therapy.

Results: Hyponatremia developed in 9 (12%) of the 75 patients after initiation of paroxetine treatment. Mean±SD time to development of hyponatremia was 9.3±4.7 days (median, 9 days; range, 1-14 days; n=8). In the multivariate regression, lower body mass index and lower baseline plasma sodium level (<138 mEq/L) were significant risk factors for the development of hyponatremia in these patients.

Conclusions: Hyponatremia is an underrecognized and potentially serious complication of paroxetine treatment in older patients. Our results provide a foundation for understanding the etiology and risk factors associated with paroxetine-induced hyponatremia.

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anorexia, nausea, fatigue, lethargy, and confusion) and are common in older patients with depression. Without proper monitoring of sodium levels in elderly patients prescribed SSRIs, these symptoms may be dismissed by health care providers as the inevitable maladies of aging, and the patient may therefore be at risk for serious sequelae. The clinical presentation of hyponatremia associated with SSRIs is often compatible with the syndrome of inappropriate antidiuretic hormone (ADH) secretion, yet ADH levels are not routinely measured to confirm this impression.

The purpose of this study, therefore, was to determine prospectively the incidence of hyponatremia in older depressed patients prescribed the SSRI paroxetine. We also identified specific patient characteristics that may account for susceptibility to paroxetine-induced hyponatremia. Finally, we sought to provide evidence of a mechanism of hyponatremia in patients prescribed paroxetine.

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 studies were conducted within the Intervention Research Center for Late Life Mood Disorders at the University of Pittsburgh, Western Psychiatric Institute and Clinic.

SUBJECTS

From August 1999 through September 2001, 94 patients provided written informed consent to participate in this research study. Only those patients who were determined to be normonatremic (plasma sodium level, ≥135 mEq/L) at baseline and who met criteria for inclusion in the antidepressant treatment protocol were eligible for entry into the present study. Of these 94 patients, 17 men and women were excluded owing to the absence of a sodium level measurement at baseline or after initiation of paroxetine treatment. Two women were excluded because they failed to meet the baseline sodium inclusion criteria. Therefore, we included in the analysis 75 men and women aged 63 through 90 years (mean ± SD age, 75.3 ± 6.0 years) who were diagnosed as having a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, major depressive episode.

ASSESSMENTS

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 Depression and a score of 18 or higher on the Folstein Mini-Mental State Examination. Medical burden was quantified by the Cumulative Illness Rating Scale–Geriatric. 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:

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

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 colleagues and subsequently modified. The intra-assay and interassay coefficients of variation range from 5% 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. 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 5 µm 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 230 ng/mL and 3.2% for 75 ng/mL. Commercially purchased analytical paroxetine controls were analyzed in every assay.

Plasma paroxetine concentrations 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.
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 symptom development 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>
<thead>
<tr>
<th>Table 1. Baseline Demographic, Clinical, and Laboratory Data for Normonatremic and Hyponatremic Patients</th>
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</thead>
<tbody>
<tr>
<td><strong>Normonatremic Patients</strong></td>
</tr>
<tr>
<td><strong>No. of Patients</strong></td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>No. (%) male</td>
</tr>
<tr>
<td>No. (%) white</td>
</tr>
<tr>
<td>BMI</td>
</tr>
<tr>
<td>CIRS-G score</td>
</tr>
<tr>
<td>17-Item Hamilton-D score</td>
</tr>
<tr>
<td>Folstein MMSE score</td>
</tr>
<tr>
<td>Sodium level, mEq/L</td>
</tr>
<tr>
<td>SUN, mg/dL</td>
</tr>
<tr>
<td>Creatinine level, mg/dL</td>
</tr>
<tr>
<td>ADH, pg/mL</td>
</tr>
<tr>
<td>Plasma osmolality, mOsm/kg</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.
hyponatremia developed remained asymptomatic or reported only mild symptoms of nausea and fatigue. However, one patient complained of confusion, disorientation, and feeling “unsteady on his feet.”

Univariate logistic regression analyses (Table 2) identified lower body mass index (BMI) and lower baseline plasma sodium level and osmolality as being associated with increased risk for development of hyponatremia in this group of patients. Using these variables and variables that we deemed important based on a review of the literature (female sex, medical burden, and cognitive function) in the multivariate logistic regression model with backwards-stepwise regression (Table 3), we identified lower BMI and lower baseline plasma sodium level to be significant independent predictors of hyponatremia.

Using receiver operating characteristics analyses, we determined that a baseline plasma sodium concentration of 138 mEq/L or less was found to predict the development of hyponatremia with 78% sensitivity and 91% specificity.

Figure 2 represents the relationship between plasma osmolality and plasma ADH levels in normonatremic and hyponatremic patients. Plasma ADH and osmolality values depicted in Figure 2 were measured a mean of 11.6±5.6 and 9.5±3.6 days from initiation of paroxetine therapy in the normonatremic and hyponatremic groups, respectively. We found a moderately strong positive correlation between plasma ADH level and plasma osmolality in the normonatremic group (Spearman ρ=0.43; P=.055). Owing to the small number of patients in the hyponatremic group, correlation analyses were not statistically reliable. Although ADH concentrations remained within the physiologic range (1-2 pg/mL [0.9-1.8 pmol/L]) in the hyponatremic group, ADH levels were not suppressed appropriately relative to the low plasma osmolality (Figure 2).

Furthermore, urinary excretion of sodium was greater than 20 mEq/L (range, 21-116 mEq/L), and urine osmolality was greater than 300 mOsm/kg (range, 329-616 mOsm/kg) in the individuals in whom hyponatremia developed.

COMMENT

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. The incidence described herein is a conservative one and is likely an underestimate, because the study by design included monitoring and preventive clinical management of plasma sodium levels. Early countermeasures may account for the transient nature of hyponatremia in some of our patients. To our knowledge, this is the first prospective evaluation of hyponatremia with 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

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>χ² 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>

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>χ² 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>3.87</td>
<td>.09</td>
</tr>
<tr>
<td>BMI</td>
<td>2.49 (0.58 to 1.06)</td>
<td>2.49</td>
<td>.11</td>
</tr>
<tr>
<td>CIRS-G total score</td>
<td>2.32 (0.49 to 1.09)</td>
<td>2.32</td>
<td>.13</td>
</tr>
<tr>
<td>Folstein MMSE‡</td>
<td>2.002 (0.57 to 1.72)</td>
<td>0.002</td>
<td>.97</td>
</tr>
<tr>
<td>Baseline sodium level</td>
<td>6.10 (0.11 to 0.78)</td>
<td>6.10</td>
<td>.01</td>
</tr>
<tr>
<td>Backwards stepwise regression</td>
<td>31.25‡</td>
<td>&lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CI, confidence interval; CIRS-G, Cumulative Illness Rating Scale–Geriatrics; Hamilton-D, Hamilton Rating Scale for Depression; 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.
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 nonsteroidal 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 hyponatremia 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 hyponatremia. 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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From the Intervention Research Center for Late Life Mood Disorders, Department of Pharmaceutical Sciences, School of Pharmacy (Drs Fabian, Amico, Kroboth, Corey, and Pollock), and the Departments of Psychiatry (Drs Fabian, Mulsant, Dew, Reynolds, and Pollock; and Mss Begley and Weber; and Mr Bensasi) and Medicine (Dr Amico), School of Medicine, University of Pittsburgh, and the Geriatric Research, Education, and Clinical Center, Veterans Affairs Pittsburgh Health System (Dr Mulsant), Pittsburgh, Pa. Dr Mulsant has received research support from Forest Laboratories, Eli Lilly, GlaxoSmithKline, and Pfizer/Eisai; consultations from Eli Lilly, Forest Laboratories, GlaxoSmithKline, and Pfizer; speakers’ fees from GlaxoSmithKline, Janssen Pharmaceutica, and Pfizer/Eisai; and honoraria from Forest Laboratories, GlaxoSmithKline, Lundbeck, and Pfizer/Eisai and owns stock in Forest Laboratories, Akzo-Nobel, and Pfizer. Dr Reynolds has received research support and honoraria from Forest Laboratories and GlaxoSmithKline. Dr Pollock has received research support from Janssen Pharmaceutica, Pfizer, and GlaxoSmithKline; consultations from Forest Laboratories, Janssen Pharmaceutica, Pharmacia & Upjohn, Organon Inc, and GlaxoSmithKline; and speakers’ fees from Forest Laboratories, Janssen Pharmaceutica, Lundbeck, Organon Inc, and GlaxoSmithKline.

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REFERENCES


