Observational Study

Medicine®

OPEN

Anxiolytic treatment but not anxiety itself causes hyponatremia among anxious patients

Mayan Gilboa, MD[a,b,*], Gideon Koren, MD[c], Racheli Katz, MSc[c], Cheli Melzer-Cohen, MSc[c], Varda Shalev, MD[b,c], Ehud Grossman, MD[a,b]

Abstract

The aim of the study was to define whether anxiety itself or only the treatment with anxiolytic medication is risk factor for hyponatremia and overhydration.

A case–control study of patients with a diagnosis of anxiety who received a selective serotonin reuptake inhibitor (SSRI). Serum sodium, urea to creatinine ratio, and odds ratio (OR) of hyponatremia and overhydration before initiation of treatment were compared to those of a control group of participants. Laboratory tests were also examined for changes following treatment with an SSRI. All blood tests were conducted from January 1, 2001 until December 31, 2017. Subjects were selected from a large electronic database, insuring 2 million Israelis. A total of 7211 patients with a diagnosis of anxiety who have received a prescription for an SSRI were identified; 3634 were excluded mostly due to other conditions that could cause hyponatremia, and 3520 participants were included in the case group. The control group consisted of 6985 age and gender matched participants who did not have a diagnosis of anxiety or any other exclusion criteria.

Mean serum sodium levels were elevated in cases before the initiation of SSRIs; sodium: case 139.3 (137.3–141.3), control 139.2 (137.06–141.26) mmol/L ($P = .01$). The OR of hyponatremia was 0.89 for the case group ($P = .004$). Treatment with SSRIs decreased mean serum sodium (139.3–139.1 mmol/L; $P = .0001$) and increased by 50% the rate of hyponatremia (2.6–3.9% $P = .024$).

It is the use of SSRIs and not anxiety itself that causes hyponatremia among anxious patients.

Abbreviations: ADH = anti-diuretic hormone, GFR = glomerular filtration rate, HMO = health maintenance organization, MHS = Macabbi Health Services, OR = odds ratio, SSRI = selective serotonin reuptake inhibitor, U/Cr = urea/creatinine.

Keywords: anxiety, hyponatremia, selective serotonin reuptake inhibitor

1. Introduction

Hyponatremia, which is defined as a serum sodium concentration <135 mM, is the most common electrolyte disorder encountered in clinical practice,[1] occurring in up to 22% of hospitalized patients.[2] It is associated with increased mortality, length of hospital stay, cognitive decline, falls, and fractures.[3,4] Defining the etiology of hyponatremia is a critical step in the management since treatment is tailored to the specific cause.[5] It is well established that selective serotonin reuptake inhibitors (SSRIs),[6–8] serotonin and noradrenaline reuptake inhibitors, and tricyclic antidepressants can cause hyponatremia.[9]

Primary polydipsia, which is also a possible etiology of hyponatremia, occurs in 5% to 25% of psychiatric patients[10,11] and is more likely to be encountered in patients with schizophrenia or mental retardation.[12] It has been previously stated that patients with anxiety disorders[13,14] particularly middle-aged women are at risk of polydipsia.[15,16] Some evidence suggest an association between psychologic stress and excessive water consumption and hyponatremia. Experimental studies have shown that mice who show anxiety, like behavior tend to overhydrate.[17] Patients with severe mental illness who were hospitalized due to self-induced water intoxication, experience considerable anxious feelings and express this as a reason for engaging in excess fluid consumption.[18]

The risk of polydipsia in anxious patients has been described in several articles, best practice guidelines, and even textbooks[17–22]; however, it has not been well established. The risk of polydipsia and hyponatremia in anxiety is important since SSRIs, which can cause hyponatremia, are becoming a very popular treatment of anxiety. It is not clear whether hyponatremia observed in anxious patients treated with SSRIs is related to the anxiety or to the treatment or to both.

We therefore designed this large population-based study to examine whether patients with anxiety disorders, before initiation of SSRIs, are more prone to hyponatremia and exhibit indirect markers of overhydration as a result of polydipsia.

2. Patients and methods

2.1. Data source and extraction

We conducted a case–control study within Macabbi Health Services electronic medical record database. Macabbi Health Services (MHS) is the 2nd largest HMO in Israel with approximately two million enrollees. We extracted patient

Editor: Zelena Dora.

The authors have no funding and conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

[a] Internal Medicine D, The Chaim Sheba Medical Center, Tel-Hashomer, [b] Sackler Faculty of Medicine, Tel Aviv University, [c] Maccabi Health Services, Institute of Research and Innovation, Tel Aviv, Israel.

[*] Correspondence: Mayan Gilboa, Internal Medicine D, The Chaim Sheba Medical Center, Tel-Hashomer, Israel (e-mail: mayangilboa@yahoo.com).

Copyright © 2019 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

Medicine (2019) 98:5(e14334)

Received: 3 November 2018 / Received in final form: 2 January 2019 / Accepted: 6 January 2019

http://dx.doi.org/10.1097/MD.0000000000014334

information including demographic data (sex and date of birth), medical diagnosis, medications, and the results of all blood tests conducted from January 1, 2001 until December 31, 2017.

Cases were MHS enrollees who were diagnosed by a mental health professional or family physician as suffering from generalized anxiety or a panic disorder as defined by International Classification of Diseases, 9th revision, codes 300.02 and 300.01, and who received at least 1 prescription of SSRI. All cases were older than age 18 years at diagnosis. To be included in this study, cases had to have had at least 1 blood serum electrolytes recorded in MHS electronic medical records before the date of the SSRI prescription, up to 6 months prior to the diagnosis of anxiety or purchase of an SSRI, the latest of the 2. The date of the laboratory test was defined as the index date; individuals who were pregnant at the time of laboratory test had another psychiatric condition, received medications, had a medical condition that could cause hyponatremia, or that their laboratory tests had features that could cause pseudohyponatremia, as described in Table 1 Supplementary Data, http://links.lww.com/MD/C787, were excluded from this group.

Control subjects were matched from all MHS database to cases based on sex and year of birth. Patients with diagnosis of anxiety or panic disorder as described earlier, or who had ever received a prescription for an SSRI (accounting for the fact that patients may receive anxiolytic medications without proper documentation of a psychiatric diagnosis) or who had exclusion criteria as described for cases were excluded. In addition, controls were required to have had at least 1 electrolyte blood test at the same age as matched cases and due to seasonal variations in sodium concentration the lab test was taken within 1 calendar month prior and 1 month after that of the case. Matching process was generated twice. In the 1st step, controls were randomly selected in 1:30 ratio based on sex and age. In the 2nd step, all other information were extracted, patients were excluded accordingly, and final population was rematched 2:1 to cases.

For subjects in the case group, a 2nd lab test obtained after 2 days and up to a year after purchasing their 1st SSRI was also taken to show the effect of SSRIs on serum sodium.

Variables of interest among lab tests included serum sodium, creatinine, and urea. Urine electrolytes taken within a 2-week interval of serum electrolytes were also obtained. Glomerular filtration rate (GFR) was calculated with the CKD-EPI equation.[19] Hyponatremia was defined as serum sodium <135 mmol/L and borderline hyponatremia was defined as serum sodium ≥ 135 and <138 mmol/L. Dehydration was defined as urea/creatinine (U/Cr) ratio above 100 and an "overhydration" was defined as U/Cr ratio below 40. All blood tests were analyzed at a single national laboratory.

$$\begin{aligned} \mathrm{CKD-Epi} = \mathrm{eGFR} &= 141 \times min\left(S_{cr}/\kappa, 1\right)^{\alpha} \times \max\left(S_{cr}/\kappa, 1\right)^{-1.209} \\ &\times 0.993^{\mathrm{Age}} \times 1.018\,[\text{if female}] \times 1.159\,[\text{if black}] \end{aligned}$$

eGFR (estimated glomerular filtration rate) = mL/min/1.73 m^2; S_{Cr} (standardized serum creatinine) = mg/dL; $\kappa = 0.7$ (females) or 0.9 (males); $\alpha = -0.329$ (females) or -0.411 (males); min = indicates the minimum of S_{Cr}/κ or 1; max = indicates the maximum of S_{Cr}/κ or 1; age = years.

The mean serum sodium, U/Cr ratio, odds ratio (OR) of hyponatremia, borderline hyponatremia, dehydration, and overhydration were compared between the case and control groups and also between the case group before and after initiation of SSRIs.

Table 1

Demographic and medical characteristics of case and controls groups.

	Case	Control	*P*-value
Number of subjects	3520	6985	
Females, n (%)	2450 (69.6%)	4875 (69.8%)	.84
Age, mean (SD)	39.61 (13.6)	39.45 (13.5)	.57
Age group			
<34	1351 (38.4%)	2698 (38.6%)	.89
35–44	977 (27.8%)	1933 (27.7%)	
45–54	667 (18.9%)	1339 (19.2%)	
55–64	343 (9.7%)	686 (9.8%)	
>65	182 (5.2%)	329 (4.7%)	
GFR, mean (SD)	102.9 (18.3)	104.2 (18.4)	<.01
GFR group, n (%)			
>90	3351 (97.7%)	6722 (98.3%)	.10
60–89	63 (1.8%)	94 (1.4%)	
45–59	12 (0.3%)	16 (0.2%)	
<44	4 (0.1%)	3 (0.0%)	
Cancer, n (%)	139 (3.9%)	88 (1.3%)	<.001
Diabetes, n (%)	105 (3.0%)	197 (2.8%)	.64
Obesity, n (%)	408 (11.6%)	865 (12.4%)	.24
Hypertension, n (%)	334 (9.5%)	506 (7.2%)	<.01
Chronic kidney disease, n (%)	80 (2.3%)	108 (1.5%)	<.01
Cardiovascular history, n (%)	176 (5.0%)	250 (3.6%)	<.01
Myocardial infarction, n (%)	32 (0.9%)	49 (0.7%)	.25
Ischemic heart disease, n (%)	52 (1.5%)	95 (1.4%)	.63
Atrial fibrillation, n (%)	21 (0.6%)	25 (0.4%)	.08
Cerebrovascular event, n (%)	8 (0.2%)	13 (0.2%)	.65
Transient ischemic attack, n (%)	11 (0.3%)	14 (0.2%)	.26
Congestive Heart Failure, n (%)	3 (0.1%)	8 (0.1%)	.66
COPD	21 (0.6%)	44 (0.6%)	.84
Osteoporosis	135 (3.8%)	240 (3.4%)	.30

Groups differed by GFR, cancer, hypertension, chronic kidney disease and all cardiovascular morbidity.
GFR = glomerular filtration rate, SD = standard deviation.

2.2. Statistical analysis

Data management and statistical analysis were performed using SPSS statistics software, version 24 (IBM, Armonk, New York). Baseline characteristics were compared between the case and control groups. The Chi-squared test was used to compare categorical variables. For continuous variables, a Shapiro–Wilk test of normality was conducted. For serum sodium, a normal distribution was demonstrated and therefore a Student *t* test was used to compare the means. The U/Cr ratio was not normally distributed and therefore the nonparametric Mann–Whitney test was used to compare the means of the 2 groups.

Multivariate logistic regression models were constructed to assess the OR of hyponatremia, borderline hyponatremia, and dehydration in the case and control groups. The multivariate models were adjusted for the baseline characteristics found to be significantly different between the groups, as shown in Table 1, including GFR group, cancer, chronic kidney disease, hypertension, and atrial fibrillation. The populations were matched for age and gender, and hence age and gender were not included in the multivariate analysis.

Subgroup analysis according to gender, age groups (below 35, 35–44, 45–54, 55–64, above 65), and GFR group (≥ 90 or <90) were also conducted.

Then effect size was calculated as well to verify if the statistical differences between groups is significant or if the *P*-value was affected by sample size. Due to the small differences between the means of the serum sodium and U/Cr ratios, although significant,

effect size was calculated as followed for all population and subgroup analyses:

$$Effect\ size = \frac{Mean(Countinuers) - mean(Discontinuers)}{SDpooled}$$

The magnitude of effect size is as followed: 0.01 = very small, 0.2 = small, 0.5 = medium, 0.8 = large, 1.2 = very large, and 2 = huge.[20]

The study was approved by the Institutional Ethics Committee of Macabbi Health Services at Assuta Hospital in Tel Aviv.

3. Results

3.1. Study population

Among 1.5 million MHS members aged 18 years old, 7211 patients had ever received a diagnosis of an anxiety disorder as described above, have ever received a prescription for an SSRI, and had at least 1 serum sodium test acquired before initiation of the SSRI and not more than 6 months before the diagnosis of anxiety or initiation of treatment (the earliest of the 2). About 3634 patients were excluded, 1128 had another psychiatric condition or a medical condition that could cause hyponatremia, 612 had abnormal lab results in their index lab data that could cause pseudohyonatremia, and 1894 received medications that could cause hyponatremia. A control group was constructed with a ratio of 30 matched subjects by age and sex for each case. Of these controls, 76,796 patients had a serum sodium test at an index date matching that of case (same age and at the same time of year + one calendric month), 22,397 were excluded for having diagnosis of a psychiatric illness (including anxiety) or received a prescription for an anxiolytic medication, 28,820 subjects were excluded for the exclusion criteria stated in the case group (1338, medical condition; 3038, suspected pseudohyponatremia; 2594, medications). Redundant controls were removed so that each case would have at least 1 control and 3465 (98%) had 2 controls. Subjects from the case group who did not have any control were removed. The final groups consisted of 3520 cases and 6985 controls (Fig. 1).

Baseline demographics and medical condition are presented in Table 1. The groups did not differ in age and gender with a mean age of 39.5 and 69% of participants female. The distribution of ages between the groups was also similar. Mean GFR was lower in the cases (102.9 mL/min) than in the controls (104.24 mL/min; $P = .001$). The prevalence of most medical conditions was similar apart from cancer (3.9% vs 1.3%, $P = .001$), hypertension (9.5% vs 7.2%, $P = .0001$), and cardiovascular disease (5% vs 3.6%, $P = .001$).

3.2. Serum sodium levels and rate of hyponatremia and hydration

The mean serum sodium in the case group and controls was 139.3 and 139.2 mmol/L in ($P = .01$), and the U/Cr ratio was 67.54 and 68.63, respectively ($P = .02$; Fig. 2A and B); the effect size for these comparisons were 0.06 for the sodium and 0.05 for the U/Cr ratio, both considered a very small effect.

The rate of borderline hyponatremia was 35.5% in cases and 37.7% in controls with an adjusted OR of 0.91 (confidence interval [CI] 0.83–0.99, $P = .027$); for true hyponatremia, the rate was 2.2% vs 3.3% with an adjusted OR 0.68 (CI 0.52–0.89,

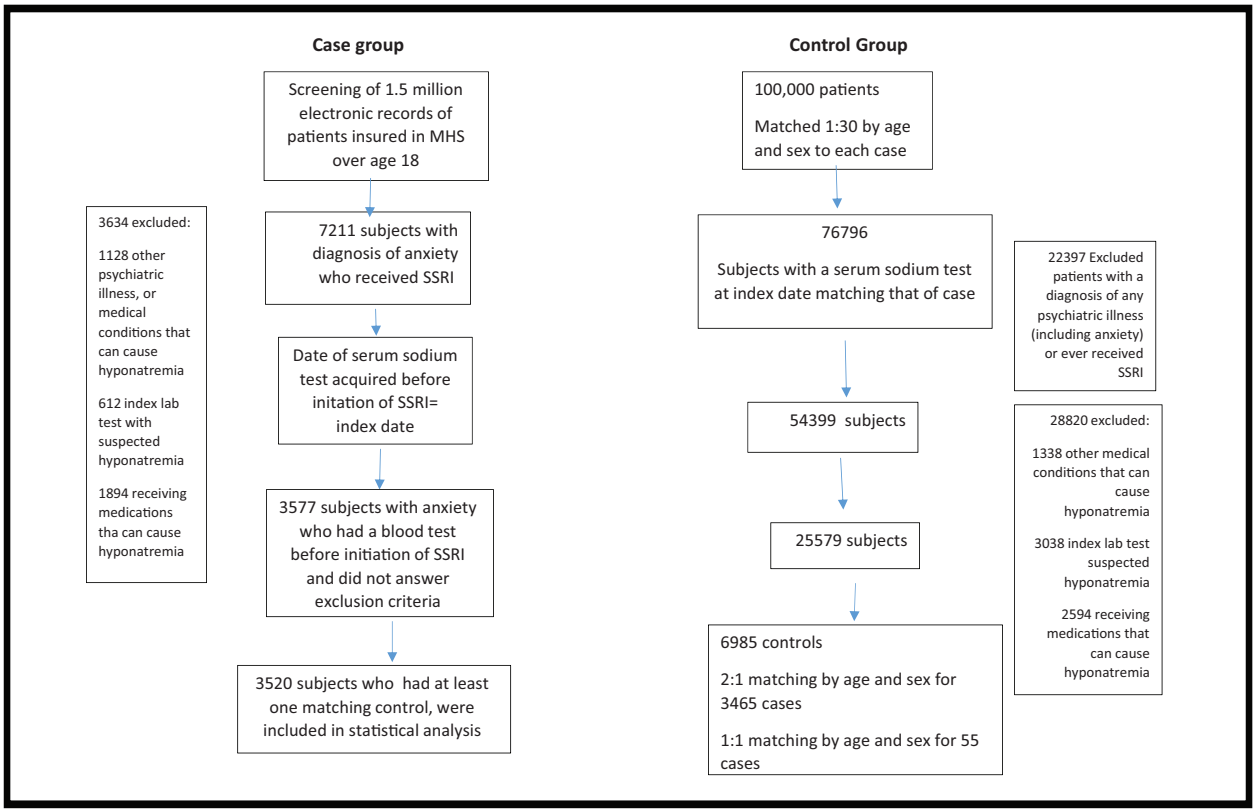

Figure 1. Constructing the case and control groups, after exclusion criteria case group consisted of 3520 subjects, 98% of them had 2 controls in the control group and the remaining 2% had only 1 case matching.

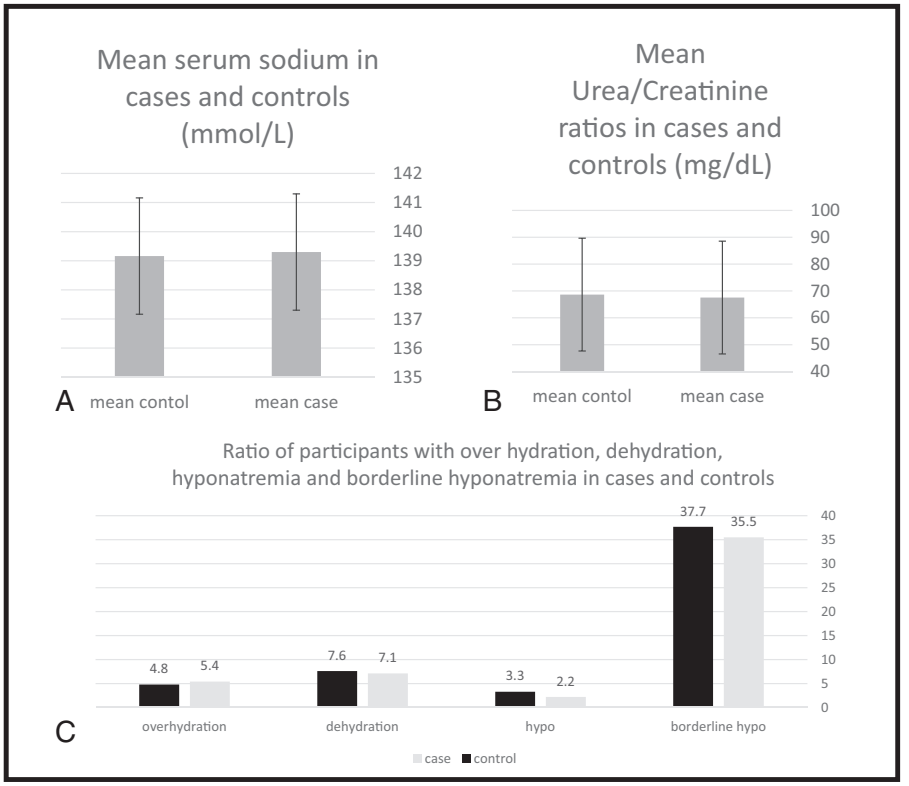

Figure 2. (A) Mean serum sodium in cases 139.3 and in controls 139.2 ($P = .01$). (B) Mean urea/creatinine ratios in cases 67.54 and in controls 68.63 ($P = .02$). (C) The ratio of participants with overhydration, dehydration, hyponatremia, and borderline hyponatremia (left to right) in cases and controls.

$P = .004$). For dehydration, the rate was 7.1% vs 7.6% with an adjusted OR of 0.88 (CI 0.75–1.04, $P = .136$), and for overhydration, the rate was 5.4% vs 4.8% with an OR of 1.16 (CI 0.96–1.4, $P = .13$; Fig. 2C). The corrected alpha was calculated with the Bonferroni equation and was 0.007, when compared to this alpha only, the OR for hyponatremia was significant and more prevalent among controls.

The same analysis was performed to males and females, by different age groups, and by normal and abnormal GFR, similar observations were noted, and no specific group demonstrated a major difference in mean sodium U/Cr ratio or OR for hyponatremia, borderline hyponatremia, overhydration, or dehydration.

3.3. Effect of selective serotonin reuptake inhibitors on serum sodium

Examining the difference between values of serum sodium before and after initiation of an SSRI among the case group revealed a statistically significant decrease (139.3–139.1, $P = .0001$), yet this difference was small and calculation of the effect size was 0.1, very small. The ratio of borderline and actual hyponatremia showed a more substantial increase in borderline hyponatremia increasing from 35.3% to 40.7%, OR = 1.15, $P = .001$, and hyponatremia increasing from 2.6% to 3.9% OR = 1.5, $P = .024$ (Fig. 3).

A subanalysis by gender, age group, GFR above and below 90, and SSRI type revealed that the increase in borderline hyponatremia was more pronounced among patients 55 to 64 years old (OR 1.3, $P = .039$), with GFR below 90 (OR 1.4, $P = .001$) and who used citalopram (OR 1.3, $P = .025$). There was no group showing a significantly increase in hyponatremia, probably due to the small number of events.

4. Discussion

In this large population-based trial, we showed that anxiety is not a risk factor for hyponatremia or of overhydration. We showed as previously described that treatment with SSRIs among anxious patients is a risk factor for hyponatremia.

Anxiety disorders are among the most common psychiatric disorders, affecting up to 15% of the general population.[21] Though patients with anxiety disorders do develop many medical conditions at a higher rate than does the general population,[22–24] symptoms previously classified as secondary to anxiety can in fact have an organic etiology, as in the case of peptic ulcer disease.[25] Classifying a medical condition as secondary to anxiety or "hysteria" is a common pit fall[26] and could be dangerous especially when treating women.[27–29] Anxiety as a risk factor for polydipsia has been mentioned in several sources. In addition, though human and animal models have shown that ADH production and release is influenced by both physiologic and psychologic stress,[5,30] anxiety has never been proved to cause polydipsia. When following the citations to discover the source of this statement 2 different studies are quoted,[31,32] yet none of these articles mentions anxiety as a risk factor for polydipsia. It is not completely clear how this unbased statement found its way into textbooks and became common knowledge, and in our study, we failed to find evidence to support this statement. This false notion that middle-aged anxious women are at risk for polydipsia could cause a physician to overlook other relevant diagnosis when evaluating such a patient.

Primary polydipsia was 1st described in patients with schizophrenia[31] and was named "psychogenic polydipsia." Psychiatric patients suffering from primary polydipsia consume excessive amounts of fluid, conventionally defined as 3 or more liters per day, though in extreme cases up to 10 or 15 L per

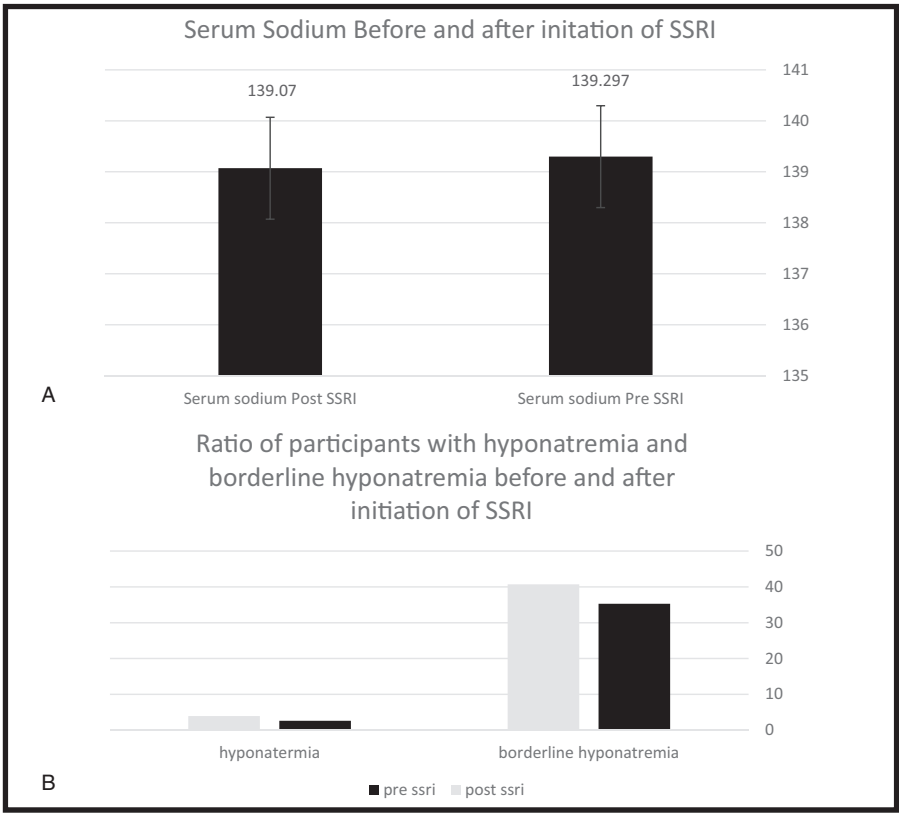

Figure 3. (A) Mean serum sodium before and after initiation of selective serotonin reuptake inhibitor (SSRI) among case group, $P = .0001$. (B) The ratio of participants with actual hyponatremia before and after initiation of SSRI 2.6% vs 3.9%, odds ratio (OR) 1.5, $P = .024$, and with borderline hyponatremia 35.3% to 40.7%, OR 1.15, $P = .001$.

day.[33] Hyponatremia secondary to polydipsia is not an obvious complication. Many regulatory mechanisms protect the serum sodium from variations in water consumption,[34] yet hyponatremia is the most dangerous and clinical important complication of polydipsia.[35,36] Furthermore, these tight regulatory mechanisms might be disturbed in elderly patients or patients with decreased renal function.[37,38] The fact that subanalysis by age groups and renal function did not demonstrate any differences in serum sodium and the ratio of hyponatremia further strength our conclusions.

Our study has several challenges that need to be acknowledged. We did not examine direct indicators of overhydration; to do this, one would need to directly question the patients about their water consumption or examine their urine osmolality (these data were available for only 10 patients in the case group and 7 patients in the control). We used indirect measures such as the U/Cr ratio; it is well established that a high ratio is mostly due to dehydration,[39] and low ratios might be suggestive of overhydration.[40] In this study, we tried to isolate anxiety as a risk factor for hyponatremia and thus we used numerous exclusion criteria, taking out any patient who might experience hyponatremia due to another etiology. Doing so we could conclude that anxiety as an isolated condition is not a risk factor for hyponatremia; yet it might theoretically be a risk factor when combined with other known etiologies for hyponatremia.

Antidepressants are common medication used by millions of people around the world. Their average consumption rate is 5% in the Organization for Economic Co-operation and Development countries[41] and is as high as 10% to 11% in some countries such as Iceland and the United States.[41,42] The SSRIs are effective in treating major depression, and are also anxiolytics with demonstrated efficacy in the treatment of generalized anxiety, panic, social anxiety, and obsessive-compulsive disorder.[43]

It is well known that SSRIs may cause hyponatremia and some large studies have shown that the prevalence of hyponatremia among patients receiving SSRIs was among 9% to 10%.[9,44] In our study, we found that the prevalence was about 4% and this difference could be due to the fact that most previous studies were conducted solely on a population of elderly patients and that SSRIs might have a synergistic effect with other factors excluded in this study. As seen in other studies, we also corroborated that citalopram is the most significant medication in decreasing serum sodium.[9] Some studies showed that switching the patient from SSRIs to mirtazapine may lower the risk of hyponatremia.[45]

In conclusion, we found that anxiety is not an isolated risk factor for hyponatremia, the increased tendency of hyponatremia among anxious patients appears only after initiation of SSRIs. We were not able to prove that anxiety in general and specifically anxiety among middle-aged women is a risk factor for overhydration.

The present study dispels an old myth that middle-aged anxious woman drink excessively, putting them at a risk for hyponatremia. It highlights the need to challenge unsubstantiated medical truism with evidence.

Author contributions

GM designed data collection tools, wrote the statistical analysis plan, cleaned and analyzed the data, and drafted and revised the paper. She is guarantor. KG, designed data collection tools, wrote

the statistical analysis plan and drafted and revised the paper. KR obtained the data. MCC wrote the statistical analysis plan, and revised the draft paper. VK designed data collection tools, and revised the draft paper. GE initiated the collaborative project, designed data collection tools, and drafted and revised the paper.
Dr Mayan Gilboa affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.
Conceptualization: Mayan Gilboa, Ehud Grossman.
Data curation: Mayan Gilboa, Racheli Katz.
Formal analysis: Mayan Gilboa.
Investigation: Mayan Gilboa.
Methodology: Mayan Gilboa, Gideon Koren, Cheli Melzer-Cohen.
Project administration: Mayan Gilboa.
Resources: Gideon Koren, Shalev Varda.
Supervision: Gideon Koren, Shalev Varda, Ehud Grossman.
Validation: Cheli Melzer-Cohen.
Writing – original draft: Mayan Gilboa.
Writing – review & editing: Gideon Koren, Ehud Grossman.
Mayan Gilboa orcid: 0000-0003-1754-7750.

References

[1] Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of hyponatremia. Am J Med 2006;119:S30–5.
[2] Dennis Kasper, Anthony Fauci, Stephen Hauser, Dan Longo, J. Larry Jameson JL. No Title. In: *Harrison's Principles of Internal Medicine*, 19;2015:298-303.
[3] Gunathilake R, Oldmeadow C, McEvoy M, et al. Mild hyponatremia is associated with impaired cognition and falls in community-dwelling older persons. J Am Geriatr Soc 2013;61:1838–9.
[4] Fehlberg EA, Lucero RJ, Weaver MT, et al. Associations between hyponatraemia, volume depletion and the risk of falls in US hospitalised patients: a case–control study. BMJ Open 2017;7:e017045.
[5] Ball SG, Iqbal Z. Diagnosis and treatment of hyponatraemia. Best Pract Res Clin Endocrinol Metab 2016;30:161–73.
[6] Bouman WP, Pinner G, Johnson H. Incidence of selective serotonin reuptake inhibitor (SSRI) induced hyponatraemia due to the syndrome of inappropriate antidiuretic hormone (SIADH) secretion in the elderly. Int J Geriatr Psychiatry 1998;13:12–5.
[7] Gandhi S, Shariff SZ, Al-Jaishi A, et al. Second-generation antidepressants and hyponatremia risk: a population-based cohort study of older adults. Am J Kidney Dis 2017;69:87–96.
[8] Grover S, Biswas P, Bhateja G, et al. Escitalopram-associated hyponatremia. Psychiatry Clin Neurosci 2007;61:132–3.
[9] Leth-Møller KB, Højmann Hansen A, Torstensson M, et al. Antidepressants and the risk of hyponatremia: a Danish register-based population study. BMJ open. 2016.
[10] de Leon J, Dadvand M, Canuso C, et al. Polydipsia and water intoxication in a long-term psychiatric hospital. Biol Psychiatry 1996;40:28–34.
[11] Llerena A, De la Rubia Martínez A, Peñas-Lledó EM. Prevalence of polydipsia and water intoxication in psychiatric inpatients [in Spanish]. Actas Esp Psiquiatr 2001;29:299–303.
[12] Mercier-Guidez E, Loas G. Polydipsia and water intoxication in 353 psychiatric inpatients: an epidemiological and psychopathological study. Eur Psychiatry 2000;15:306–11.
[13] Sailer C, Winzeler B, Christ-Crain M. Primary polydipsia in the medical and psychiatric patient: characteristics, complications and therapy. Swiss Med Wkly 2017;147:w14514.
[14] Kohli A, Verma S Jr, Sharma AJr. Psychogenic polydipsia. Indian J Psychiatry 2011;53:166–7.
[15] Srinavasan S, Narasimhan M. Psychogenic polydipsia. BMJ best Pract 2017;5.
[16] Irwin Richard S, Rippe James M. Irwin and Rippe's Intensive Care Medicine - Google Books. 6th ed. Philadelphia, PA: Lippincott Williams &Wilkins; 2008.
[17] Goto T, Kubota Y, Tanaka Y, et al. Subchronic and mild social defeat stress accelerates food intake and body weight gain with polydipsia-like features in mice. Behav Brain Res 2014;270:339–48.
[18] May DL. Patient perceptions of self-induced water intoxication. Arch Psychiatr Nurs 1995;9:295–304.
[19] Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–12.
[20] Sawilowsky SS. New effect size rules of thumb. J Mod Appl Stat Methods 2009;8:597–9.
[21] Shelton RC. Chapter 19. Anxiety disorders. In: Ebert MH, Loosen PT, Nurcombe B, Leckman JF, eds. CURRENT Diagnosis & Treatment: Psychiatry, 2nd ed. New York, NY: The McGraw-Hill Companies; 2008.
[22] Bowen RC, Senthilselvan A, Barale A. Physical illness as an outcome of chronic anxiety disorders. Can J Psychiatry 2000;45:459–64.
[23] Culpepper L. Generalized anxiety disorder and medical illness. J Clin Psychiatry 2009;70:20–4.
[24] Hoge EA, Ivkovic A, Fricchione GL. Generalized anxiety disorder: diagnosis and treatment. BMJ 2012;345:e7500.
[25] Malfertheiner P, Chan FKL, Mccoll KEL. Peptic ulcer disease. The Lancet; 2009.
[26] Stone J, Smyth R, Carson A, et al. Systematic review of misdiagnosis of conversion symptoms and "hysteria". BMJ 2005;331:989.
[27] Bönte M, von dem Knesebeck O, Siegrist J, et al. Women and men with coronary heart disease in three countries: are they treated differently? Womens Health Issues 2008;18:191–8.
[28] Frich JC, Malterud K, Fugelli P. Women at risk of coronary heart disease experience barriers to diagnosis and treatment: a qualitative interview study. Scand J Prim Health Care 2006;24:38–43.
[29] Pope JH, Aufderheide TP, Ruthazer R, et al. Missed diagnoses of acute cardiac ischemia in the emergency department. N Engl J Med 2000; 342:1163–70.
[30] Scantamburlo G, Ansseau M, Legros JJ. Role of the neurohypophysis in psychological stress [in French]. Encephale 2001;27:245–59.
[31] Illowsky BP, Kirch DG. Polydipsia and hyponatremia in psychiatric patients. Am J Psychiatry 1988;145:675–83.
[32] Hariprasad MK, Eisinger RP, Nadler IM, et al. Hyponatremia in psychogenic polydipsia. Arch Intern Med 1980;140:1639–42.
[33] Dundas B, Harris M, Narasimhan M. Psychogenic polydipsia review: etiology, differential, and treatment. Curr Psychiatry Rep 2007;9: 236–41.
[34] Stanhewicz AE, Larry Kenney W. Determinants of water and sodium intake and output. Nutr Rev 2015;73:73–82.
[35] Verghese C, de Leon J, Josiassen RC. Problems and progress in the diagnosis and treatment of polydipsia and hyponatremia. Schizophr Bull 1996;22:455–64.
[36] Bhatia MS, Goyal A, Saha R, et al. Psychogenic polydipsia - management challenges. Shanghai Arch psychiatry 2017;29:180–3.
[37] Davis PJ, Davis FB. Water excretion in the elderly. Endocrinol Metab Clin North Am 1987;16:867–75.
[38] Merrill JP. The excretion of water and solutes in renal failure. Trans Am Clin Climatol Assoc 1954;66:178–91.
[39] Morgan DB, Carver ME, Payne RB. Plasma creatinine and urea: creatinine ratio in patients with raised plasma urea. Br Med J 1977; 2:929–32.
[40] Lumand G, Leat-Khourl S. Significance of low serum urea nitrogen concentrations. Clin Chem 1989;354:639–40.
[41] OECD. Health at a Glance 2011: OECD Indicators. Paris; 2011. http://www.oecd.org/health/health-systems/health-at-a-glance-19991312.htm
[42] Pratt LA, Brody DJ, Gu Q. Antidepressant Use in Persons Aged 12 and Over: United States, 2005–2008 Key findings. 2005. https://www.cdc.gov/nchs/data/databriefs/db76.pdf. Accessed March 19, 2018.
[43] O'Donnell JM, Bies RR, Shelton RC. Drug therapy of depression and anxiety disorders. In Brunton LL, Hilal-Dandan R, Knollmann BC, eds. Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 13 ed. New York, NY: McGraw-Hill Education; 2017.
[44] Mannesse CK, Jansen PAF, Van Marum RJ, et al. Characteristics, prevalence, risk factors, and underlying mechanism of hyponatremia in elderly patients treated with antidepressants: a cross-sectional study. Maturitas 2013;76:357–63.
[45] Mogi T, Yoshino A, Ikemoto G, et al. Mirtazapine as an alternative for selective-serotonin-reuptake-inhibitor-induced syndrome of inappropriate secretion of antidiuretic hormone. Psychiatry Clin Neurosci 2012;66:80.