

Hyponatremia Secondary to Antidepressant Therapy - A Post Marketing Safety Study

Harsha M Shetty^{1*}, Manimekalai K², Sivaprakash B³, Jagan Mohan R² and Pooja H Shetty⁴

¹Clinical Trials Unit, JCU School of Medicine, James Cook University, Cairns, QLD, Australia

²Department of Pharmacology, Mahatma Gandhi Medical College and Research Institute, Pillaiyarkuppam, Pondicherry, India

³Department of Psychiatry, Mahatma Gandhi Medical College and Research Institute, Pillaiyarkuppam, Pondicherry, India

⁴Remote Area Mental Health Services, Cairns and Hinterland Hospital and Health Services, Queensland Health, Cairns, QLD, Australia

Abstract

Background: Most antidepressants have been associated with hyponatremia. The risk is highest during the early stages of the treatment. Symptoms are commonly mistaken for physical complaints of old age or the underlying conditions. Speed of onset determines the risk of developing symptoms.

Aims and Objectives: To establish the incidence, risk factors, time course of detection of hyponatremia complicating treatment with antidepressant therapy. Also, to objectively assess the causality, severity and preventability of hyponatremia as an adverse drug reaction.

Methods: The study was carried out in collaboration between the Departments of Pharmacology and Psychiatry, Mahatma Gandhi Medical College and Research Institute, India. The source populations in our study were all the out- and in-patients on antidepressant therapy with normal serum sodium concentration meeting the eligibility criteria of the study. The assessment of causality, severity and preventability of the hyponatremia with the use of anti-depressant therapy were assessed using Naranjo's scale, Hartwig and Siegel's scale, and Schumock and Thornton's scale respectively.

Results: A total of 24 cases had hyponatremia with 21 cases assessed as "probable" on Naranjo's Scale. We found a moderately strong positive correlation between the use of mirtazapine and occurrence of hyponatremia with a p value of 0.089. The use of venlafaxine also suggested a positive correlation with a p value of 0.097. Though not statistically significant we found cases reported for Milnacipran. Mean \pm SD for overall time to detection of hyponatremia was 224.71 ± 117.79 days. In the univariate regression, we found SNRIs and Mirtazapine to have significant association with hyponatremia. However, none of the other factors and concomitant medications proved to have a significant association on multivariate regression analysis.

Conclusion: Hyponatremia is an under recognized and potentially serious complication of antidepressant therapy. Our results provide a foundation for understanding the safety profile of antidepressants in a clinical setting of hyponatremia and its impact on suitable monitoring and treatment strategy.

Keywords: Pharmacovigilance; Drug safety; Anti-Depressants; Hyponatremia

Introduction

The safety of drugs is of paramount importance to patients and healthcare professionals. The consequences of a new drug having a potentially serious safety profile are quite significant for patients, healthcare professionals and the pharmaceutical industry. There have been many drugs that were very promising in terms of their benefit risk profile and benefited thousands of patients but were later found to have serious side effects, resulting in their withdrawal [1]. A commonly quoted Meta-analysis performed in the United States indicates that adverse drug reactions (ADRs) were between the 4th and 6th most common cause of death in 1997. Much less is known about the situation in low-income countries. The lack of awareness amongst the health care professionals about the magnitude of drug-related problems is a mystery. The main reason is probably that the drug-related injuries are not always obvious, immediate and visible outside the natural course of the underlying disease. They often manifest themselves gradually and with symptoms similar to those caused by common diseases, sometimes while patients are at home [2].

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems. One of the ways to carry out the pharmacovigilance activities are through investigator initiated post

authorization safety studies/post marketing surveillance studies. These are scientifically rigorous studies of a product or a class that is approved for registration in a particular country, designed to produce reliable information about the drug safety. It is a well-established fact that pre-marketing clinical trials do not have the statistical power to detect rare ADRs nor do they have significant follow-up to identify delayed ADRs or effects from long-term exposure. In view of this, pharmacovigilance plays a prominent role in establishing the safety profile of marketed drugs [3]. No degree of care and caution at the pre-clinical and clinical testing stages can guarantee an absolute safety when a product is marketed and prescribed in large populations with settings different from the clinical trials [4]. This study was a sincere attempt from the research team to contribute significantly to the pharmacovigilance

***Corresponding author:** Harsha M Shetty, Research Officer, Clinical Trials Unit, JCU School of Medicine, Level 2, Block A, Cairns Hospital, PO Box 902, The Esplanade, Cairns, QLD 4870, Australia, Tel: +61 0488091933; E-mail: harsha.mahabalashetty@jcu.edu.au

Received May 28, 2015; Accepted June 09, 2015; Published June 17, 2015

Citation: Shetty HM, Manimekalai K, Sivaprakash B, Jagan Mohan R, Shetty PH (2015) Hyponatremia Secondary to Antidepressant Therapy - A Post Marketing Safety Study. J Pharmacovigilance 3: 167. doi:[10.4172/2329-6887.1000167](https://doi.org/10.4172/2329-6887.1000167)

Copyright: © 2015 Shetty HM, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

and safety profile of the antidepressants in a real world scenario and to objectively establish hyponatremia as ADR in a clinical setting.

Hyponatremia is a clinical complication of a wide variety of diseases, surgical procedures, and drug treatments. When defined as plasma sodium concentration of less than 135mEq/L, the prevalence amongst inpatients could be as high as 15 to 30%. It was interesting to note that the admissions were unrelated to hyponatremia and this was identified as an incidental finding or of iatrogenic origin [5]. Additionally, the prevalence of hyponatremia of acute hyponatremia was 0.8% [6]. Most antidepressants have been associated with hyponatremia. The mechanism of this adverse effect is probably the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) [7]. This syndrome consists of faulty urine dilution in the presence of plasma osmolality and is considered as an osmo-regulatory disorder [8]. The causes of this syndrome are usually divided into four main categories, which include neoplasms, central nervous system disorders, lung diseases and medications. The main symptoms are usually non-specific and range from mild lethargy, anorexia, insomnia, fatigue, nausea, muscle cramps, headache and confusion, even leading upto coma [9]. The previous drug utilization studies have found depressive disorders as being one of the most commonly encountered clinical conditions in a psychiatric setting [10]. With antidepressant drugs being one of the most commonly prescribed drugs, hyponatremia due to antidepressant therapy is potentially a serious adverse effect that demands careful and strategic monitoring, particularly in those patients at greatest risk. The objectives of the study were to study the incidence of hyponatremia in patients who are receiving antidepressant medications in our setting, identification of all possible risk factors which contribute to occurrence of hyponatremia in such patients, to identify the time course of detection of hyponatremia in patients while on antidepressant therapy and to compare the results of this study with the existing percentage of risk of hyponatremia due to antidepressants.

Materials and Methods

This prospective observational study was carried out in collaboration with The Departments of Pharmacology and Psychiatry, Mahatma Gandhi Medical College and Research Institute; which offers psychiatric services to the population of Puducherry, Cuddalore, Villupuram and nearby places in India. The source population in our study was all the out- and in-patients on antidepressant therapy meeting the eligibility criteria of the study. They mainly represent the rural and low-income segment of the population in this area. The Institutional Human Ethics Committee (IHEC) of Sri Balaji Vidyapeeth University, Puducherry, approved the study with the ethical standards of the Declaration of Helsinki of 1975 that was with last amendments, Edinburgh (2000); Seoul (2008) and Fortaleza (2013). The patients inducted in the study were all aged more than 18 years of age, who were prescribed antidepressant therapy for the first time and were willing to give the informed consent. Patients who were hyponatremic (Plasma sodium level less than 135meq/L) at the baseline and who were prescribed additional antipsychotic medications excluded from the study.

Since from Jan to Dec 2009, 84 subjects requiring anti-depressant therapy as per the diagnosis under ICD-10 diagnostic criteria; provided the written informed consent to participate in the research study. Six men and two women were excluded from the study owing to the absence of the plasma sodium measurement level at baseline and after the initiation of the antidepressant therapy. Two women were excluded because they failed to meet the baseline sodium inclusion criteria. Subjects were followed up to a minimum period of 3 months and with a maximum period of 6 months.

In order to adjust the factors that confound the association between the use of anti-depressants and hyponatremia, all the potentially important co-variates like age, socio economic status, co morbid medical conditions and their concomitant medications were included in the case report form. Plasma sodium level measurements were carried out before initiating the antidepressant therapy and then at every stipulated visit or monthly, whichever is earlier for a minimum period of three months. Noting the date of sodium level measurements including the first recorded low plasma sodium concentration approximated the time between the start of the drug therapy to the development of hyponatremia. The times of resolution of the hyponatremia after the respective treatments were also noted. Though the mechanism for developing hyponatremia due to anti-depressant therapy is mainly attributed to SIADH, all the laboratory investigations necessary to rule out this were not carried out keeping patient's affordability as a factor. But the cause of hyponatremia being from SIADH was confirmed based on the treatment given for the patient. We notified the patient's consultant psychiatrist regarding the development of hyponatremia and discussed a suggested plan for the management of the same.

Patients' compliance to the anti-depressant medications was elicited as a part of routine psychiatric evaluation at every visit. All the reported symptoms (e.g. lethargy and fatigue) and other adverse events were documented at every visit and were evaluated at monthly review meetings between the co-investigators.

The assessment of causality, severity and preventability of the hyponatremia with the use of anti-depressant therapy were assessed using Naranjo's scale, Hartwig's scale and Thornton and Schumock's scale respectively.

Statistical Analysis

Descriptive statistics were used to summarize the demographic, clinical and laboratory variables. Results on continuous measurements were represented as Mean \pm SD (Min-Max) and results on categorical measurements were represented in Numbers (%). Significance was assessed at 5 % level of significance. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups. 95% Confidence Interval has been computed to find the significant features. Confidence Interval with lower limit more than 50% was considered to be statistically significant.

After the completion of the study, patients were classified into 1 of the following 2 groups: hyponatremic (plasma sodium measurement \leq 135meq/L) and normonatremic (plasma sodium measurement \geq 135meq/L). Univariate logistic regressions were performed to examine the group differences with respect to baseline, clinical and laboratory measures. We then performed multivariate logistic regression analysis using age, sex, medical burden and all the variables identified in univariate logistic regression analysis that were significant at $p<0.05$. Data on co-morbidities were not available for all the subjects. For those missing values, dummy variables were created and entered into multivariate logistic regression model. Student t test (two tailed, dependent) has been used to find the significance of study parameters on continuous scale within each group. All the statistical calculations were carried out with SPSS statistical package (Version 17.0).

Note on the basis of interpretation:

Odds Ratio=OR

OR<1: Negatively related

OR=1: Not related

OR>1: Positively related

Significant figures

+Suggestive significance (P value: 0.05 < P < 0.10)

*Moderately significant (P value: 0.01 < P ≤ 0.05)

**Strongly significant (P value: P ≤ 0.01)

Results and Discussion

The results of the study indicate that hyponatremia is one of the significant complications of antidepressant therapy, which mandates robust monitoring of the patients while on therapy for better outcomes. Prior evidence of this association originates mainly from case reports, case control studies and review articles. Hyponatremia has been reported as a complication of antidepressant therapy mainly with Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin and Nor-epinephrine Reuptake Inhibitors (SNRIs) [11]. There have been reports of 811 cases of hyponatremia induced by SSRIs as compared to 163 with non-SSRIs as per FDAs spontaneous reporting system database between Jan 1966 to December 1999 [12]. Our study was a prospective clinical safety study with total of 74 patients with age ranging from 18-65 years. A total of 24 patients (32.4%) had serum sodium level less than 135mEq/L while on antidepressant therapy and were considered as potential cases of hyponatremia. Most patients who developed hyponatremia were in the age group of 21 to 40 years (Table 1).

Although heterogeneity in the data makes it difficult to establish the incidence of this adverse event or compare the risks associated with different drugs, there have been attempts to analyze this in an objective fashion. We identified an overall incidence of hyponatremia of 32.4% irrespective of the various classes. Paroxetine, Desvenlafaxine, Duloxetine, Escitalopram, Milnacipran, Mirtazapine, Sertraline and Venlafaxine were the drugs for which hyponatremia was identified as an adverse event. Amongst these drugs, Mirtazapine and Venlafaxine were found to have statistically significant association (Table 2). Though not statistically significant we identified 3 cases of hyponatremia with the use of Milnacipran, which has not been reported so far. In few studies, though usages of some of these drugs have led to serious complications due to hyponatremia, an overall statistically significant association could not be established in our study due to the small sample size. In order to determine the effect of the drugs along with the presence of other covariates the drugs were regrouped as follows.

Class A (SSRIs): Escitalopram, Fluvoxamine, Paroxetine and Sertraline

Class B (SNRIs): Venlafaxine, Desvenlafaxine, Duloxetine and Milnacipran

Class C (Others): Mirtazapine, Trazadone and Dothiepin

Table 3 shows the distribution of the patients of hyponatremia among the different drug classes. We found a moderately positive correlation between the occurrences of hyponatremia with the Class C drugs with a p value of 0.028. This was mainly due to the drug Mirtazapine present in Class C, which caused hyponatremia in this group. Also, a suggestive positive correlation was found between the hyponatremia and Class B drugs, which were mainly SNRIs. In contrast to the literature where maximum incidences have been found with SSRIs, we found statistically significant results with respect to SNRIs and Mirtazapine; though SSRIs accounted for almost 50% of the cases as compared to 45.8% due to SNRIs and 4.2% due to Mirtazapine [11]. This should be cautiously interpreted as it could

be attributed to greater use of SSRIs as compared to other drugs. The incidence described herein is a conservative one and is likely to be an underestimate, because the study by design included monitoring and preventive clinical management of dropping plasma sodium levels.

Unlike other previous studies where incidences were identified by most of the cases reported against a particular group of drugs or cases derived from spontaneous reports, published cases and post-marketing surveillance; this study was undertaken with strict eligibility criteria where objective analysis of adverse drug reaction was made before noting the incidence and the risk factors [12-14]. The literature review suggested old age, female sex, low body weight, concomitant drug treatments (e.g. diuretics, Non-Steroidal Anti-inflammatory Drugs (NSAIDs) if used in a renal compromise patient, carbamazepine, antipsychotics, mood stabilizers, desmopressin, antiepileptics, cancer chemotherapy like vincristine), reduced renal function (especially acute and chronic renal failure and pyelonephritis), medical comorbidity (e.g. hypothyroidism, diabetes, Chronic Obstructive Pulmonary Disease (COPD), hypertension, Heart Failure, circulating volume depletion, hormonal imbalances, Head Injury, Cerebrovascular Accidents and various cancers) and warm weather as factors influencing the occurrence of hyponatremia [15-17]. Within the study group, the most commonly encountered psychiatric diagnosis was Moderate depression without somatic syndrome (F32.10) followed by Dysthymia (F34.10) and severe depression without psychotic symptoms (F32.2) as shown in the Table 4. Surprisingly, we found a moderately strong positive correlation between recurrent depressive disorder (F33) and the occurrence of hyponatremia in the patients with a p value of 0.031 followed by F32.10, which also suggested significance with a p value of 0.053. In order to determine the effect of individual co-morbid conditions and concomitant medication on the occurrence of hyponatremia, complete break up analysis of the above factors were considered and no statistically significant results were obtained to

Age in years	Number of patients (n=74)	Hyponatremia		P value
		Absent (n=50)	Present (n=24)	
18-20	5 (6.8%)	4 (8%)	1 (4.2%)	1.000
21-30	28 (37.8%)	17 (34%)	11 (45.8%)	0.443
31-40	29 (39.2%)	20 (40%)	9 (37.5%)	1.000
41-50	5 (6.8%)	4 (8%)	1 (4.2%)	1.000
51-60	5 (6.8%)	4 (8%)	1 (4.2%)	1.000
>60	2 (2.7%)	1 (2%)	1 (4.2%)	0.546

Table 1: Age Distribution of the patients.

Antidepressants	Number of patients (n=74)	Hyponatremia		P value
		Absent (n=50)	Present (n=24)	
1.Desvenlafaxine	2 (2.7%)	0 (0%)	2 (8.3%)	0.102
2.Doxipen	1 (1.4%)	1 (2%)	-	1.000
3.Duloxetine	11 (14.9%)	8 (16%)	3 (12.5%)	1.000
4.Escitalopram	22 (29.7%)	17 (34%)	5 (20.8%)	0.289
5.Fluvoxamine	2 (2.7%)	2 (4%)	-	1.000
6.Milnacipran	6 (8.1%)	3 (6%)	3 (12.5%)	0.382
7.Mirtazapine	12 (16.2%)	11 (22%)	1 (4.2%)	0.089*
8.Paroxetine	8 (10.8%)	4 (8%)	4 (16.7%)	0.424
9.Sertraline	5 (6.8%)	2 (4%)	3 (12.5%)	0.321
10.Trazadone	1 (1.4%)	1 (2%)	-	1.000
11.Venlafaxine	4 (5.4%)	1 (2%)	3 (12.5%)	0.097+

Table 2: Distribution of antidepressants among patients with incidence of hyponatremia

Class of Antidepressants	Number of patients (n=74)	Hyponatremia		P value
		Absent (n=50)	Present (n=24)	
Class A	37(50.0%)	25(50.0%)	12(50.0%)	1.000
Class B	23(31.1%)	12(24.0%)	11(45.8%)	0.067+
Class C	14(18.9%)	13(26.0%)	1(4.2%)	0.028*
Total	74(100.0%)	50(100.0%)	24(100.0%)	-

Table 3: Class of Antidepressants and Incidence of Hyponatremia.

ICD10 diagnosis	Number of patients (n=74)	Hyponatremia		P value
		Absent (n=50)	Present (n=24)	
F32.10	21 (28.4%)	18 (36%)	3 (12.5%)	0.053+
F32.11	2 (2.7%)	1 (2%)	1 (4.2%)	0.546
F32.2	11 (14.9%)	8 (16%)	3 (12.5%)	1.000
F33	3 (4.1%)	0	3 (12.5%)	0.031*
F34.1	14 (18.9%)	10 (20%)	4 (16.7%)	1.000
F41.1	6 (8.1%)	3 (6%)	3 (12.5%)	0.682
F41.2	10 (13.5%)	6 (12%)	4 (16.7%)	0.719
F41.9	2 (2.7%)	1 (2%)	1 (4.2%)	0.546
F42	4 (5.4%)	3 (6%)	1 (4.2%)	1.000
F45.1	1 (1.4%)	-	1 (4.2%)	0.324

Moderate depression without somatic syndrome (F32.10); Moderate depression with somatic syndrome (F32.11); Severe depression without psychotic symptoms (F32.2); Recurrent depressive disorder (F33); Dysthymia (F34.1); Generalised Anxiety Disorder (F41.1); Mixed Anxiety and Depressive Disorder (F41.2); Anxiety Disorder Unspecified (F41.9); Obsessive Compulsive Disorder (F42); Undifferentiated Somatoform Disorder (F45.1).

Table 4: ICD10 diagnosis distribution of patients studied with incidence of hyponatremia.

prove the causal role of the above factors influencing the occurrence of hyponatremia. A univariate and multivariate logistic regression analysis controlled for the confounding covariates were carried out. Univariate regression analysis in table 18 identified a moderately positive correlation between the occurrence of hyponatremia and Class C drugs (Mirtazapine) with a p value of 0.026. We also identified Class B drugs, which suggested a positive correlation with a p value of 0.057. None of the other covariates contributed significantly to risk of developing hyponatremia. The multivariate analysis (Table 5) showed no statistically significant association between any of the covariates and the occurrence of hyponatremia. Ideally a large post authorization safety study should be undertaken, but we believe that this study is an important first step towards analyzing further management especially with regard to monitoring of patients keeping risk factors in mind.

The symptoms of hyponatremia can easily be mistaken for non-specific symptoms associated with depression. These are not always looked for and hence more often than not is detected accidentally. As the early symptoms are vague and nonspecific, and even may mimic the underlying psychiatric disorder, an attempt was made to record these symptoms. We identified the documented symptoms and assessed these symptoms on a case-by-case basis. These non-specific symptoms mimicking the complaints of depression were reported in 4 patients in the hyponatremic group. Table 6 shows the symptoms of the hyponatremia along with the respective serum sodium concentration during the same visit of detection. Few of these symptoms which were common to both hyponatremia and depression; like fatigability, lethargy, and tiredness were present among those patients in our study group who were diagnosed to have hyponatremia. Although the cause of hyponatremia was not confirmed by laboratory measures; since most of our patients improved with fluid restriction and dose reduction,

and with symptoms pointing towards hypotonic hyponatremia, we can make an assumption that the cause could be SIADH in line with evidence from the literature review.

Hyponatremia induced by antidepressants may occur within a day or may take up to several months, following initiation of drug therapy. The highest incidence is in the first few weeks of the treatment [11]. Since the visits of patients in our study were scheduled with respect to the treatment of their underlying condition and the convenience of the patients, the time of detection of hyponatremia was identified as one of our data points for analysis. The overall mean time of detection of the hyponatremia due to antidepressant therapy was 224 days, which falls in the range quoted by one of the studies earlier [11]. Paroxetine group was detected as early as 154 days and Mirtazapine group as late as 428 days. Class wise, SSRI mean time of detection ranged from 212.25 ± 136.01 days as compared to SNRI mean detection time of 218.73 ± 85.04 days. Though the data falls under the range quoted in earlier studies, this should be cautiously interpreted as the visits scheduled for the patients were based on the underlying condition and not based on the occurrence of hyponatremia [13,18]. Figure 1 shows the classes of antidepressant drugs and their respective time of detection.

The hyponatremia as an ADR was assessed based on three parameters namely causality relationship, severity of the ADR and preventability of the ADR. These parameters are the three essential factors in standard analysis of any adverse event. Due to ethical considerations, patients were not subjected to rechallenge with their respective drugs. To overcome this, assessment of hyponatremia as an adverse drug reaction were carried out using Naranjo's Algorithm for causality, Hartwig's scale for severity and Schumock and Thornton scale for preventability. Table 7 shows the results of the assessments of the ADRs based on these parameters.

Variables	Hyponatremia		Multivariate		
	No (n=50)	Yes (n=24)	P value	OR	95%CI
Age <35 years	29(58.0%)	13(54.2%)	Reference		
Age >35 years	21(42.0%)	11(45.8%)	0.807	0.87	0.27-2.77
Female	28(56.0%)	14(58.3%)	Reference		
Male	22(44.0%)	10(41.7%)	0.935	0.95	0.29-3.09
Income > INR 3000	19(38.0%)	10(41.7%)	Reference		
Income < INR 3000	31(62.0%)	14(58.3%)	0.830	1.14	0.36-3.63
Absence Medical history	39(78.0%)	17(70.8%)	Reference		
Presence Medical history	11(22.0%)	7(29.2%)	0.804	0.703	0.04-11.44
Psy Con Meds	44(88.0%)	21(87.5%)	0.547	0.601	0.12-3.15
Non Psy Con Meds	9(18.0%)	7(29.2%)	0.635	1.99	0.12-34.45
Class A	25(50.0%)	12(50.0%)	Reference		
Class B	12(24.0%)	11(45.8%)	0.193	2.18	0.67-7.08
Class C	13(26.0%)	1(4.2%)	0.120	0.17	0.02-1.58

Table 5: Multivariate analysis for prediction of hyponatremia.

ADR-Symptoms	Number of patients (n=24)	Serum Sodium levels (mEq/L)
No	20	-
Yes	4	-
Fatigability+Lethargy	1	132
Anhedonia+ Fatigability+Lethargy+Sad mood	1	128
Lethargy+Tiredness	1	110
Anhedonia+Fatigability+Lethargy+Tiredness	1	123

Table 6: Symptoms of the Hyponatremia.

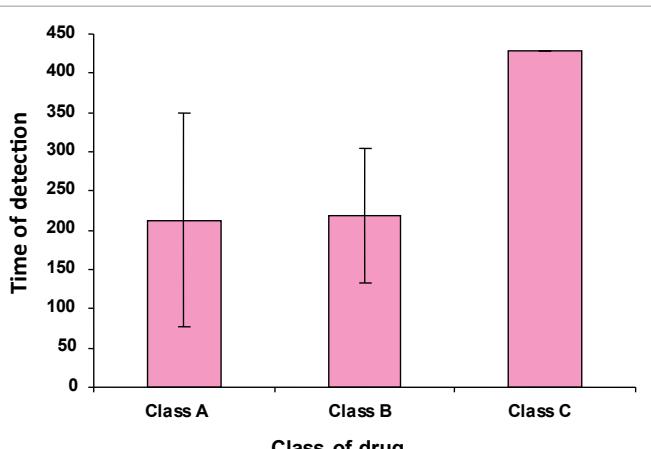


Figure 1: Time of detection of Hyponatremia.

Causal Relationship, Severity and Preventable	Number of patients (n=24)	%	95%CI
Causal Relationship			
• Probable	21	87.5	69.0-95.66
• Possible	3	12.5	4.34-31.08
Severity			
• Moderate-Level3	22	91.7	74.15-97.66
• Moderate-Level4b	2	8.3	2.32-25.85
Preventable			
• Probably Preventable	24	100.0	86.20-100.0
• Non-Preventable	0	0.0	-

Table 7: Hyponatremia- Causal Relationship, Severity and Preventability.

Conclusion

Although antidepressants are considered to be relatively safe drugs, at times they can cause serious adverse events. There is a need for awareness of the nature of development of this serious and potentially fatal complication in high-risk patients. Routine monitoring of electrolyte levels in patients, especially during the initial 2–4 weeks of therapy, may be worthwhile. There is some evidence, although not convincing, to suggest that if a patient develops hyponatremia with an SSRI, all other SSRIs should also be avoided in future. Few case reports also suggest that, in patients with hyponatremia secondary to treatment with SSRIs, the possibilities for substitution with other antidepressant drugs may be limited because of a possible increased risk of recurrence of hyponatremia [19]. Clinicians, therefore, have to be aware of the possible development of hyponatremia and SIADH when patients are placed on SSRIs or SNRIs, and serum sodium concentrations should be monitored not only in the initial few weeks of therapy, but also during the entire course for early detection and treatment of hyponatremia. Most clinicians do not realize how commonly serotonergic antidepressant drugs induce hyponatremia, because associated symptoms are nonspecific and are interpreted as either symptoms of depression (e.g., fatigue, anorexia, confusion) or medication side effects (e.g., fatigue, nausea). 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 patients will have a significant public health impact by reduction of mortality, morbidity and health care costs associated with preventable adverse medical events.

We recommend monitoring sodium and Blood Urea Nitrogen levels before initiating treatment with antidepressants and at 1 and 2 weeks after initiation of treatment. This is especially important for patients who present with additional risk factors. At minimum, a serum sodium level should be measured in all patients who exhibit abrupt changes in mental status (eg, lethargy or confusion) any time during treatment with an antidepressant. If hyponatremia develops and continuation antidepressant therapy is desired, long-term restriction of daily fluid intake has been mildly successful, although patient compliance is often poor. Failure to respond to fluid restriction warrants dose reduction and discontinuation of the causative medication until sodium levels normalize. For restarting the treatment, consider Electroconvulsive therapy or prescribe a medication from a different antidepressant class. Begin with a low dose, increasing slowly, and monitor closely. If hyponatremia recurs and continued antidepressant use is essential, consider water restriction and/or careful use of demeclocycline [20].

To the best of our knowledge, this study is one amongst the few prospective evaluations that have been done of antidepressant-induced hyponatremia trying to postulate the overall burden due to hyponatremia. The results should be cautiously interpreted owing to low sample size and the design, which is based on the clinical identification, prevention and monitoring rather than studying the natural course of the event. Such post marketing safety studies are warranted across various therapeutic areas to generate the data and to streamline the management protocols; thus promoting evidence based medicine suiting the local requirements.

Acknowledgements

The authors thank the support rendered by the patients at the participating hospital. Also, thankful to Dr. Kingshuk Lahon, Dr. Reena Verma, Dr. Shivamurthy N, Dr. Padmavathi S and the staff and postgraduate trainees of the Departments of Pharmacology and Psychiatry along with Medical Records Division of Mahatma Gandhi Medical College and Research Institute, Puducherry, India.

References

- Fitzgerald P (2008) Pharmacovigilance inspections. Indian J Pharmacol 40: vs21-23.
- Olsson S (2008) Pharmacovigilance training with focus on India. Indian J Pharmacol 40: S28-30.
- Yadav S (2008) Status of adverse drug reaction monitoring and pharmacovigilance in selected countries. Indian J Pharmacol 40: S4-9.
- Arora D (2008) Pharmacovigilance obligations of the pharmaceutical companies in India. Indian J Pharmacol 40: S13-16.
- Schrier RW (2006) Body water homeostasis: clinical disorders of urinary dilution and concentration. J Am Soc Nephrol 17: 1820-1832.
- Hsu YJ, Chiu JS, Lu KC, Chau T, Lin SH (2005) Biochemical and etiological characteristics of acute hyponatremia in the emergency department. J Emerg Med 29: 369-374.
- O J Bogunovic, J Sotelo, S Madhusoodhan (2003) Hyponatremia secondary to antidepressants. Psychiatric Annals May 33(5): 333-339.
- Belton K, Thomas SHL (2000) Drug induced syndrome of inappropriate antidiuretic hormone secretion. Postgrad Med J 76: 318.
- Cury LH, Kitadai FT, Helou CM (2006) Antidepressant-induced hyponatremia. Clinics (Sao Paulo) 61: 579-580.
- Lahon K, Shetty HM, Paramel A, Sharma G (2012) Adverse drug reaction monitoring of antipsychotics, antidepressants and mood stabilizers in the psychiatric outpatient unit of a teaching hospital – a retrospective study. International Journal of Pharma and Biosciences 3: 470-478.
- Moving KL, Leufkens HG, Lenderink AW, van den Akker VG, Hodiamont PP, et al. (2002) Association between antidepressant drug use and hyponatraemia: a case-control study. Br J Clin Pharmacol 53: 363-369.

12. Spigset O, Hedenmalm K (1997) Hyponatremia in relation to treatment with antidepressants: a survey of reports in the World Health Organization data base for spontaneous reporting of adverse drug reactions. *Pharmacotherapy* 17: 348-352.
13. Liu BA, Mittmann N, Knowles SR, Shear NH (1996) Hyponatremia and the syndrome of inappropriate secretion of antidiuretic hormone associated with the use of selective serotonin reuptake inhibitors: a review of spontaneous reports. *Can Med Med Assoc J* 155: 519-527.
14. Boyd IW (1998) Comment: hyponatremia with venlafaxine. *Ann Pharmacother* 32: 981-982.
15. Kirchner V, Silver LE, Kelly CA (1998) Selective serotonin reuptake inhibitors and hyponatraemia: review and proposed mechanisms in the elderly. *J Psychopharmacol* 12: 396-400.
16. Jacob S, Spinler SA (2006) Hyponatremia associated with selective serotonin-reuptake inhibitors in older adults. *Ann Pharmacother* 40: 1618-1622.
17. Krüger S, Lindstaedt M (2007) Duloxetine and hyponatremia: a report of 5 cases. *J Clin Psychopharmacol* 27: 101-104.
18. Wilkinson TJ, Begg EJ, Winter AC, Sainsbury R (1999) Incidence and risk factors for hyponatraemia following treatment with fluoxetine or paroxetine in elderly people. *Br J Clin Pharmacol* 47: 211-217.
19. Strachan J, Shepherd J (1998) Hyponatraemia associated with the use of selective serotonin re-uptake inhibitors. *Aust N Z J Psychiatry* 32: 295-298.
20. Stahl SM (2008) Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications. Cambridge, New York 511-667.