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# Clinical Monitoring of Various SSRI's for their Drug Induced Hyponatremia in Hospitalized Psychiatric Patients

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**A B S T R A C T**

Hyponatremia is a rare complication of the anti-depressant selective serotonin reuptake inhibitor therapy affecting early stages of treatment. The clinical monitoring of the serum natremic levels is done to identify the development of hyponatemia associated with the use of SSRI anti-depressants. The mechanism of hyponatremia is thought to be the syndrome of inappropriate secretion of anti-diuretic hormone. Hyponatremia and SIADH can cause such complications as seizure, coma, and rarely death for SSRI users. To clinically monitor hyponatremia induced by use of SSRIs in psychiatric patients and its risk factors and to identify the time duration resulting in hyponatremia of each individual drug. The study was carried out in the department of psychiatry in Pushpagiri Medical College, Kerala. The source population were the in-patients on SSRI therapy with normal serum sodium concentration, meeting eligibility criteria of the study. The depression in the patients are confirmed by Hamilton rating scale for depression and major (ICD-10) depression inventory and hospital anxiety and depression scale. The residual blood samples of the patients were collected on $2^{nd}$, $6^{th}$ and $10^{th}$ day of treatment and analyzed for serum sodium concentration. We found a moderately strong positive correlation between the use of SSRIs and occurrence of hyponatremia with a p value of .026.Mean ± SD for overall time to detection of hyponatremia was 134.6182± 1.96 days. Medication adherence improved after patient counselling by significant rate. Main symptoms of hyponatremia were identified during the study. Hyponatremia is an under recognized and potentially serious complication of SSRI therapy. The results provide a foundation for understanding the safety profile of anti-depressants in a clinical setting of hyponatremia and its impact on suitable monitoring and treatment strategy.

## Introduction

The safety of the drugs is very important to both healthcare providers and patients. Though many drugs have found its worth, 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 (Fitzgerald, 2008). The main reason for this is that the drug related injuries are not always obvious, immediate and visible outside the natural cause of underlying disease. Manifesting themselves gradually with symptoms similar to those caused by common diseases, they remain unnoticed. Selective serotonin reuptake inhibitor (SSRI) antidepressants have become increasingly popular in the treatment of depression because they have different side-effects from other classes of antidepressants. Anticholinergic side-effects, urinary hesitancy, cardiotoxicity and/or postural hypotension associated with tricyclic antidepressant use may contribute to the greater use of SSRI antidepressants in the elderly.

The risk of developing hyponatraemia while on an SSRI seems to increase with age, female, sex, previous history of hyponatraemia and the concomitant use of other medications known to include hyponatraemia (Pillans and Coulter, 1994). The mechanism of hyponatraemia is thought to be the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) (Liu, *et al.*, 1996). Data from World Health organization database for spontaneous reporting of adverse drug reactions suggest that the risk of anti-depressant associated hyponatremia is higher in women, in elderly, during the summer and during the first weeks of treatment. Women are at greater risk of hyponatraemia (Adverse Drug Reactions Advisory Committee, 1996; Abbott, 1983) Low body weight is the greater risk factor for hyponatremia complicating SSRI antidepressant use.

## Materials and Methods

This prospective observational study was carried out in collaboration with the departments of Psychiatry, Pushpagiri Medical College and Research Institute; which offers psychiatric services to the population of Thiruvalla and nearby places in India. The source population in our study was all in-patients on antidepressant SSRI therapy meeting the eligibility criteria of the study. The Institutional Human Ethics Committee (IHEC) of Pushpagiri College of Pharmacy, Thiruvalla approved the study with the ethical standards. 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 were excluded from the study.

Since from Dec 2015 to May 2016, 57 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. 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, 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 6th day and 10th day. 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. 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 also notified the patient's consultant psychiatrist regarding the development of hyponatremia. Patients' compliance to the anti-depressant medications was elicited as a part of routine psychiatric evaluation at every visit using the Morisky medication taking adherence scale-8 and counselled about the benefits of regular intake of medicines.. All the reported symptoms (e.g. lethargy and fatigue) and other adverse events were documented at every visit.

## Results and Discussion

The results of the study indicates that hyponatremia is one of the significant complications of antidepressant therapy, which mandates daily monitoring of the patients while on therapy for better outcomes. Prior evidence of this association originates mainly from case reports, case control studies, research and review articles. Hyponatremia has been reported as a complication of antidepressant therapy mainly with SSRIs and SNRIs. 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. Our study was a prospective clinical safety study with total of 55 patients with age ranging from 21 to 80years. A total of 17 patients (30.90%) 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 61-70 years (Table 1).

Paroxetine, Escitalopram, Sertraline and Fluoxetine were the drugs for which hyponatremia was identified as an adverse event. Amongst these drugs, Escitalopram and Sertraline were found to have statistically significant association with p value less than 0.05 by Chi Square Test (Table 3).

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. The literature review suggested old age, female sex, low body weight, medical comorbidity (e.g. hypothyroidism, diabetes, Chronic Obstructive Pulmonary Disease (COPD), hypertension, Heart Failure, circulating volume depletion, hormonal imbalances, concomitant drug treatments, carbamazepine, antipsychotics, mood stabilizers, antiepileptics, cancer chemotherapy like vincristine), reduced renal function (especially acute and chronic renal failure and pyelonephritis), Head Injury, Cerebrovascular Accidents and various cancers) and warm weather as the factors influencing the incidence of hyponatremia.

**Table.1** Age distribution of patients

| Age in years | Number of patients (n=55) | Hyponatremia | |
|---|---|---|---|
| | | Absent (n=38) | Present (n=17) |
| 21-30 | 4 | 2 | 2 |
| 31-40 | 14 | 13 | 1 |
| 41-50 | 13 | 11 | 2 |
| 51-60 | 11 | 9 | 2 |
| 61-70 | 9 | 2 | 7 |
| 71-80 | 4 | 1 | 3 |

**Table.2** Distribution of patients below and above 50

| | | Drug | | | | Total |
|---|---|---|---|---|---|---|
| | | Escitalopram | Fluoxetine | Paroxetine | Sertraline | |
| Age | Above 50 | 7 | 0 | 0 | 5 | 12 |
| | Below 50 | 33 | 2 | 3 | 5 | 43 |
| Total | | 40 | 2 | 3 | 10 | 55 |

**Table.3** Distribution of SSRI antidepressants among patients with incidence of hyponatremia

| Antidepressants | Number of patients (n=55) | Hyponatremia | |
|---|---|---|---|
| | | Absent (n=38) | Present (n=17) |
| 1.Escitalopram | 40 (72.7%) | 33(86.84%) | 7 (41.17%) |
| 2.Fluoxetine | 2 (3.6%) | 2 (5.2%) | 0 |
| 3.Paroxetine | 3 (5.5 %) | 2 (5.2%) | 1 (5.8%) |
| 4.Sertraline | 10 (18.2%) | 1(5.8%) | 9 (52.9%) |

**Table.4** Symptoms of the Hyponatremia

| ADR-Symptoms | Number of patients (n=55) |
|---|---|
| Fatigability+ constipation | 3 |
| Anhedonia+ Sad mood+ headache | 3 |
| Lethargy+ tiredness+ anhedonia+ sad mood | 2 |
| loss of balance+ anorexia+ constipation | 12 |

**Table.5** Distribution of patients according to time of detection of hyponatremia

| Time of Detection | | | | | |
|---|---|---|---|---|---|
| | | Frequency | Percent | Valid Percent | Cumulative Percent |
| Valid | not detected | 38 | 69.1 | 69.1 | 69.1 |
| | detected 6th day | 12 | 21.8 | 21.8 | 90.9 |
| | detected 10th day | 5 | 9.1 | 9.1 | 100.0 |
| | Total | 55 | 100.0 | 100.0 | |

**Fig.1** Age distribution of patients according to drug and age

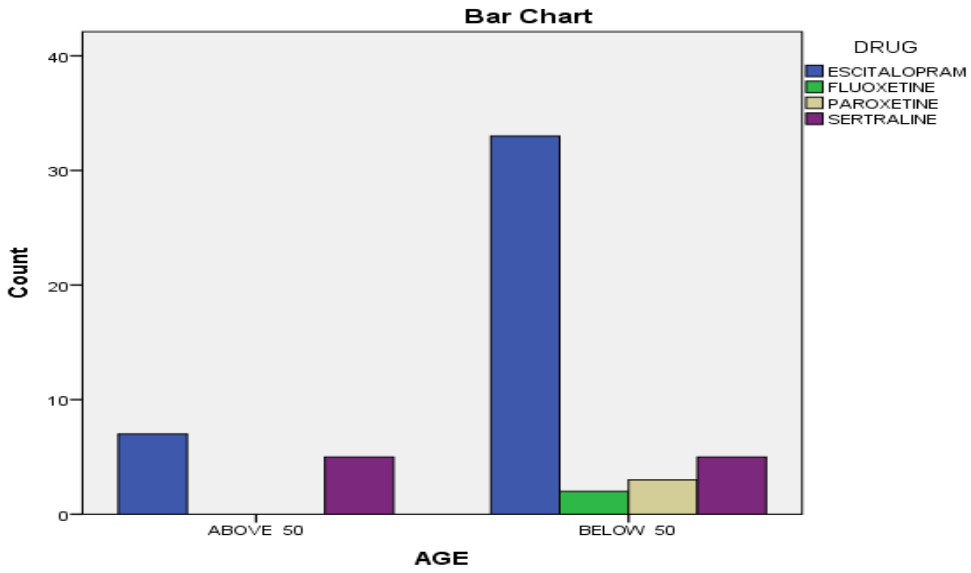



**Fig.2** Distribution of symptoms in patients taking SSRI anti-depressants

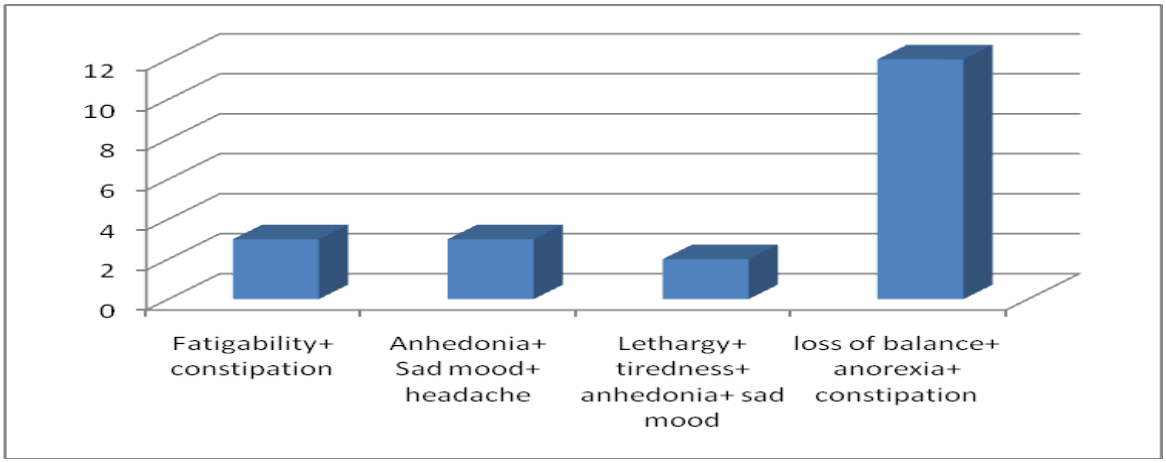


**Fig.3** Distribution of patients according to time of detection of hyponatremia

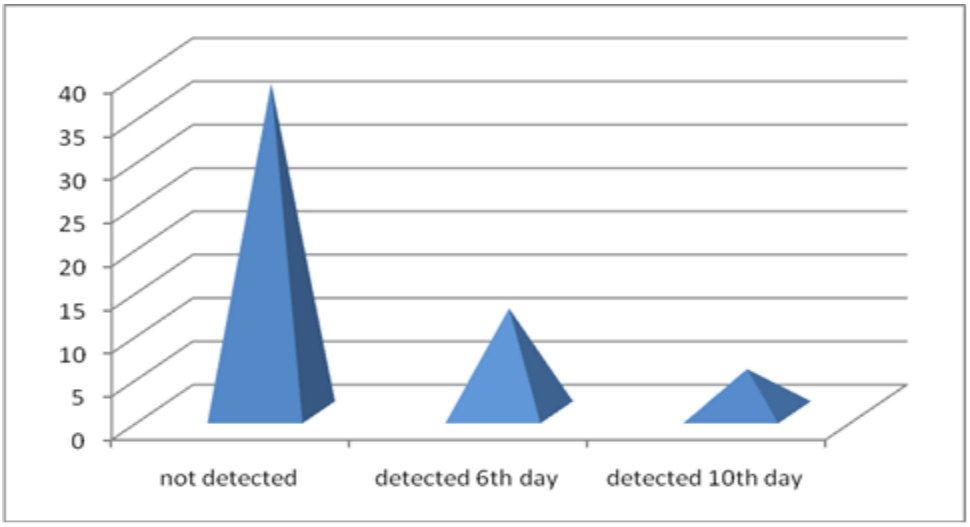
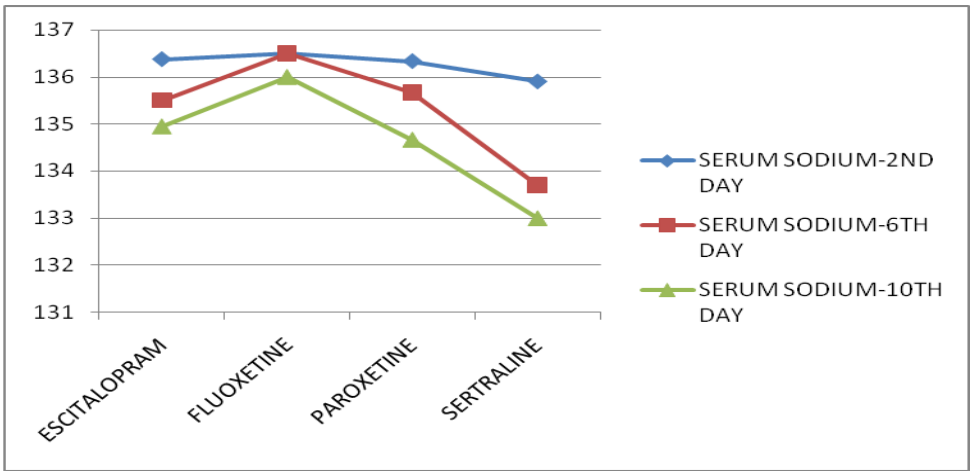



**Fig.4** Individual SSRI drug distribution according to time of detection of hyponatremia




The symptoms of hyponatremia are mistaken for nonspecific depression symptoms. As the early symptoms are non specific and vague, and may mimic the underlying psychiatric disorder, an attempt was made to record these symptoms in the patients under study.

In the present study 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 12 patients in the hyponatremic group. Table 4 shows the symptoms of the hyponatremia. 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. Figure.2 shows the distribution of patients showing symptoms.

Hyponatremia induced by antidepressants may occur within a day or several months, following initiation of drug therapy. The highest incidence is in the first few weeks of the treatment. The change in the serum sodium levels were most found in the tenth day in paroxetine and sertraline. The lowest serum sodium levels were found in sertraline causing hyponatremia complication. This was accompanied by the symptoms such as fatigue, loss of balance, anorexia and constipation.

## Conclusion

Antidepressants are considered to be relatively safe drugs, though they cause serious adverse events. The need for awareness of the development of this fatal complication in high-risk patients is important. Routine monitoring of electrolyte levels in patients, especially during the initial 1-3 weeks of therapy is necessary. 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 (Strachan J, Shepherd, 1998). Clinicianshave to be aware of the possible development of hyponatr-emia and SIADH when patients are placed on SSRIs, and serum sodium concentrations should be monitored not only in the initial few weeks of therapy, but also during the full course for early detection and treatment of this hyponatremia. 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.

At the 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 in the patient and the continuation of antidepressant is necessary then, long term restriction of daily fluid intake has been mildly successful. Failure to respond to fluid restriction warrants dose reduction and discontinuation of the causative medication until the sodium levels normalize. If hyponatremia recurs and continued antidepressant use is essential, consider either water restriction and/or careful use of demeclocycline (Stahl, 2008).

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## References

Abbott R. Hyponatremia due to antidepressant medications. Annual of Emergency Medicine. 1983; 12:708–710.

Adverse Drug Reactions Advisory Committee. Selective serotonin reuptake inhibitors and SIADH. Medical Journal of Australia. 1996; 164:562

Fitzgerald P (2008) Pharmacovigilance inspections. Indian J Pharmacol 40: vS21-23.

Liu BA, Mittmann N, Knowles SR, Shear NH. Hyponatraemia and the syndrome of inappropriate secretion of antidiuretic hormone associated with the use of selective serotonin reuptake inhibitors: a review of spontaneous reports. Canadian Medical Association Journal. 1996; 155:519–527.

Pillans PI, Coulter DM. Fluoxetine and hyponatraemia-a potential hazard in the elderly. New Zealand Medical Journal. 1994; 107:85–86.

Stahl SM. 2008. Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications. Cambridge, New York 511-667.

Strachan J, Shepherd J. 1998. Hyponatraemia associated with the use of selective serotonin re-uptake inhibitors. Aust N Z J Psychiatry 32: 295-298.

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