

## Serum Sodium Changes in Fluoxetine Users at Different Age Groups

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**Objective:** Fluoxetine, a widely used antidepressant, can affect the serum sodium level. The aim of this study was to evaluate and compare changes in the serum sodium level of depressive patients taking fluoxetine according to age.

**Methods:** This quasi-experimental study was conducted on 126 patients with depression, dividing the patients into two age groups of 15 to 35 years, and above 55 years, who referred to psychiatric clinics of the Isfahan University of Medical Sciences. Serum sodium level was measured prior to fluoxetine therapy and at the first and third week after; adverse symptoms were recorded. Serum sodium level, hyponatremia, and other adverse effects were compared between the two age groups.

**Results:** There was a significant decrease in serum sodium levels in the older patients at the first and third week after the therapy; but the serum sodium levels decreased only after the third week of therapy in the younger patients ( $p < 0.05$ ). Serum sodium level was significantly lower in older than in younger patients at the third week of the therapy ( $140.8 \pm 2.26$  vs.  $135.2 \pm 2.06$ ;  $p < 0.05$ ), and hyponatremia was detected only in the older patients after the first and third week of therapy, 4.7% and 15.8%, respectively.

**Conclusions:** Using fluoxetine can decrease serum sodium level, which is more frequent, more severe, and more clinically manifested in older than younger patients. Monitoring serum sodium level is recommended in early weeks of fluoxetine therapy especially for patients older than 55 years of age.

**Keywords:** *Elderly, Fluoxetine, Hyponatremia, Inappropriate ADH Syndrome*

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Selective serotonin reuptake inhibitors (SSRIs) are among the most common antidepressants that are increasingly used by young, adult, and elderly patients (1). Fluoxetine is a SSRI with good efficacy, few adverse effects, long half life, good compliance, and low depression relapse rate after it is discontinued, and it is also a drug of choice in elderly depressive patients (1,2). Recent studies have reported that hyponatremia and syndrome of inappropriate anti-diuretic hormone (SIADH) are more frequent in fluoxetine than in other SSRIs users (3-5), and in older patients than in younger ones (4-7). The incidence of hyponatremia in elderly patients treated with fluoxetine is 5/1000 per year (8) that reaches to maximum of 8/1000 in elderly women (7). Hyponatremia and SIADH can cause such complications as seizure, coma, and rarely death for fluoxetine users (6,9,10).

The prevalence of hyponatremia in Iranian patients with depression, who may have different drug metabolism and take fluoxetine, is still unclear. Our aim was to compare side effects of fluoxetine therapy through any changes in the serum sodium level, and its adverse symptoms in patients at different age groups.

### Materials and Methods

In a quasi-experimental study with stratified random sampling method, patients with depression referring to Sadeghieeh Elderly House and psychiatric clinics of Noor University Hospital, Isfahan (IRAN) were selected. Inclusion criteria were as follows: age between 15 and 35 or above 55 years; indication for fluoxetine prescription (20 mg/d) due to new onset depression (1); and new administration of fluoxetine. Patients with history of previous SSRI therapy, those using other psychiatric or diuretic drugs, and those with known diseases affecting serum sodium level (e.g. impaired renal function, heart failure, hypothyroidism, etc.) were not included. Compliance of the patients was checked by their associate physicians, and non-compliant patients were excluded.

In a single clinical laboratory, serum sodium level was tested for each patient before fluoxetine administration and at first and third week after fluoxetine therapy. The study was approved by Research Ethics Committee of the Isfahan University of Medical Sciences, and consent was obtained from all patients. Findings were analyzed into two age groups: patients 15 to 35 years,

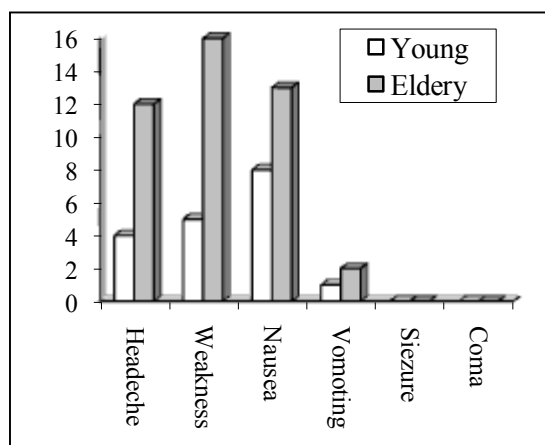


Figure 1. Hyponatremia-like symptoms findings

and patients above 55 years of age. Data were analyzed using the SPSS software version 13.5. Paired *t*-Test was used to assess fluoxetine effects on the serum sodium level in each group; and Independent Sample *t*-Test and Chi-Square Test were used to compare the serum sodium levels and the frequency of hyponatremia between the two groups.

## Results

During the study period, 158 patients entered the study; of whom, 32 patients were excluded due to irregular drug consumption. Finally, data of 126 patients (63 patients in each mentioned age group) were considered for analyses. Serum sodium levels of the patients are presented in Table 1. There was a significant decrease in serum sodium level of the older patients after first and third week of fluoxetine therapy ( $p < 0.05$ ). However, the serum sodium level decreased only after the third week of therapy in younger patients. It should be mentioned that serum sodium level did not reach to hyponatremia in none of the younger patients;  $\text{Na} < 135 \text{ mEq/l}$  (Table 2). As presented in Figure 1, the change in serum sodium level of younger patients did not accompany significant clinical manifestations. In the older group, however, decrease of sodium level was accompanied by significantly more clinical manifestations.

The frequency of serum sodium levels in each group is presented in Table 2. In the older patients' group, 3 (4.7%) and 10 (15.8%) patients experienced hyponatremia after the first and the third week of the therapy. However, no one in the younger patients' group experienced hyponatremia;  $p < 0.05$  and  $p < 0.001$ , respectively.

Table 1. Serum sodium level in fluoxetine users through the study

	Baseline	1 <sup>st</sup> week	3 <sup>rd</sup> week	P
Young, n = 63	141.6 (1.48)	141.3 (2.25)	140.8 (2.26)	Baseline to 1 <sup>st</sup> week: $p > 0.05$ <sup>b</sup> Baseline to 3 <sup>rd</sup> week: $p < 0.05$ <sup>b</sup>
Elder, n = 63	139.8 (1.31)	138.4 (2)	135.2 (2.06)	Baseline to 1 <sup>st</sup> week: $p < 0.05$ <sup>b</sup> Baseline to 3 <sup>rd</sup> week: $p < 0.05$ <sup>b</sup>
P	$p > 0.05$ <sup>a</sup>	$p > 0.05$ <sup>a</sup>	$p < 0.05$ <sup>a</sup>	

Data are shown as mean (mEq/l) (SD)

<sup>a</sup>Independent Sample *t*-Test

<sup>b</sup>Paired *t*-test

Table 2. Serum sodium level after 1 week and 3 weeks fluoxetine therapy

	1 <sup>st</sup> week		3 <sup>rd</sup> week	
	Young n = 63	Elder n = 63	Young n = 63	Elder n = 63
Serum Na (mEq/l)				
128	0	0	0	1 (1.6)
129	0	0	0	1 (1.6)
130	0	0	0	1 (1.6)
131	0	0	0	2 (3.2)
132	0	0	0	1 (1.6)
133	0	1 (1.6)	0	2 (3.2)
134	0	2 (3.2)	0	2 (3.2)
Total	0	3 (4.7)	0	10 (15.8)
P Value <sup>a</sup>		$P < 0.05$		$P < 0.001$
Serum Na = 135 mEq/l	1 (1.6)	0	0	19 (30.2)
Serum Na > 135 mEq/l	62 (98.4)	60 (95.2)	63 (100)	34 (53.9)

Data are shown as number (%)

<sup>a</sup>Chi-Square Test

## Discussion

The results of the present study showed a significant decrease in the serum sodium level of the patients after fluoxetine therapy. However, hyponatremia only occurred in older patients aged > 55 years; and patients within 15 to 35 years of age did not experience a clinically significant decrease in the serum sodium level at the first or third week after the fluoxetine therapy. These results were consistent with other studies which have shown that in 74% to 85% of the cases, fluoxetine induced hyponatremia occurs in patients within 65 to 70 years age range (3-5,7); but it is not frequent in young patients (8,11,12).

Various studies have reported different frequencies of hyponatremia (25% to 50%) in fluoxetine users (9,13). We found hyponatremia in 4.7% of the patients at the first week after the therapy and in 15.8% of the patients at the third week after the therapy in older patients. In other reports, in fluoxetine users, hyponatremia was more frequent at the second week of fluoxetine consumption, within the first to fourth week (3,4,7,10,13-16). Considering drug metabolism and different brands of drugs, these differences may be related to differences in the studied population.

The etiologies of SSRI induced hyponatremia are unclear. Hyponatremia has been detected in 3% to 5% of chronic psychiatric patients (9). Many risk factors are proposed for such hyponatremia as additional drug consumption that affects serum sodium level (e.g. diuretics) (7,12,16,17), other co-morbidities or chronic diseases such as neoplasm and schizophrenia (7,12), low body weight (9), and history of hyponatremia or polydipsia (7). Some evidence has shown that oldness is not a risk factor for the incidence of hyponatremia, and may other co-morbidities or psychiatric drugs and diuretics be suspected in this regard (17). Nevertheless, as these cases had been excluded in our study, we believe that age is an important risk factor for SSRI induced hyponatremia.

Hyponatremia may be manifested with symptoms of headache, blurred vision, polydipsia, weakness, cramps, tremor, impaired gait, nausea, vomiting, seizure, confusion, and coma (9,18). In the present study, we observed weakness, nausea, headache, and vomiting among our patients (Figure 1). The frequency of these manifestations are various among different populations (19). Most of these symptoms are non-specific and difficult to be distinguished from depression's symptoms or signs that may lead to miss management (18). Relying only on symptoms for detecting hyponatremia may lead to under-diagnosing this important complication of fluoxetine therapy; therefore, routine and frequent testing for serum sodium level is recommended specially for older patients.

This study has some limitations. First of all, the age range in this study did not include patients with 35 to 55 years of age. We did not evaluate this age range as it belongs to transition from adulthood to elderliness that may decrease the study power. It would have been

more beneficial to consider this age range and to do multivariate analyses to control age as a continuous variable; however, then we would have needed a larger sample size. In addition, ruling out concurrent diseases and drugs with known effects on the serum sodium level was based only on the patients' history. It would have been best if we checked them with a more objective measure such as renal function tests. The confounding factors of dietary intake of sodium should also be mentioned in the future studies.

## Conclusions

Using fluoxetine can decrease serum sodium level which is more frequent and more severe in elder patients, and can lead to clinically important hyponatremia in elders. Physicians should be aware of the possible development of hyponatremia and should pay more attention to clinical symptoms. Therefore, we suggest monitoring the serum sodium level in early weeks of fluoxetine therapy, especially for elder patients.

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