

# Effect of selenium as an adjunctive therapy in patients with treatment-resistant obsessive-compulsive disorder: A pilot randomized double blind placebo-controlled clinical trial

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## Summary

**Background:** The first line medicinal treatment of obsessive-compulsive disorder (OCD) includes selective serotonin reuptake inhibitors (SSRIs). Researchers have shown that there is a correlation between a deficiency of trace elements, the trace elements deficiency such as selenium, and mental disorders and mood. – Since selenium is a safe supplement with a favorable side effect profile, it may be useful as an adjunctive treatment with SSRIs.

**Aim:** To determine if adjunctive selenium therapy improves symptoms in treatment-resistant OCD.

**Methods:** Thirty-two patients with treatment-resistant OCD were selected and randomly assigned to two groups: intervention and control, with both groups continuing to receive SSRI drugs according to current guidelines. The intervention group received one 200 mcg selenium capsule daily while the control group received one placebo capsule each day for 6 weeks.

**Results:** Y-BOCS scores decreased at the end of the sixth week in both groups, but this reduction was significantly lower in the selenium group ( $P = 0.01$ ). Selenium was well tolerated and there was no significant difference between the two groups in the incidence of side effects.

**Conclusion:** The results of this study indicate that selenium, as an adjunctive treatment with SSRIs, improves symptoms of OCD and thus can be used as a new drug for treatment-resistant OCD.

**obsessive-compulsive disorder, selenium, clinical trial, pilot study**

## INTRODUCTION

Selenium is a mineral substance and trace element, and the thirty-fourth element of the periodic table of elements in nature. This element is an essential component of selenoproteins, which play an important role in many physiological functions of the body, such as antioxidant defense, the production of thyroid hor-

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mones, DNA synthesis, fertility, and reproduction. Selenium in the body can convert to many metabolites, such as methylselenol, which plays a role in preventing cancer. Selenium acts as a strong antioxidant along with vitamin E to prevent oxidative degradation in the body. Furthermore, selenium regulates iodine metabolism and also plays a role in muscle function by increasing its tolerance and strength. Another role of selenium is the reduction of the aging process [1, 2]. Selenocysteine is a component of selenoproteins that is necessary for the catalyzing function of the following enzymes: glutathione peroxidase (reduces peroxides and improves male fertility performance), iodothyronine deiodinase (regulates the activity of thyroid hormones), thioredoxin reductase (involved in the regeneration of antioxidant system, gene expression regulation, stability and cellular proliferation) and methionine reductase (degraded methionine repair) [3]. Selenium also plays an important role in the brain and the central nervous system (CNS). Grey matter is selenium-rich, while white matter has less selenium content [4, 5]. When the amount of selenium in the body is limited, the brain is the last organ to deplete its stores and when selenium starts to accumulate again in the body, it is first allocated to the brain. [3, 4]. Studies have shown that selenium bonds with proteins in the brain [8]. The amount of selenium in people's blood in different parts of the world varies depending on the quantity found in the soil and as a result of the diet. The level of selenium is considered an indicator of its long-term magnitude, and its level does not fluctuate significantly from day to day. [9]. Selenium has been shown to be effective in improving mood and other psychological aspects of the brain [10]. For instance, selenium deficiency in the brain is associated with reduced cognitive function [11] and ingesting low levels of selenium through diet can increase the likelihood of major depressive disorder [12, 13]. In a clinical trial, selenium supplementation during pregnancy reduced the risk of postpartum depression in pregnant women [14]. The inverse relationship between selenium levels and symptoms of depression is mainly related to cognitive function [15]. Furthermore, in one study, selenium was shown to reduce the anxiety of people taking HIV+ drugs [16]. In another study, sele-

nium in the form of sodium selenite has been shown to have anti-depressant and anti-anxiety effects after acute treatment in mice [17]. Selenium deficiency is also associated with schizophrenia and Alzheimer's disease [5-7, 18]. Selenium is essential for thyroid function, and there is a relationship between thyroid function and mood, behavior, and recognition [19-21]. Therefore, the relationship between selenium and thyroid function can be the cause of the positive effect of selenium on the nervous system and mental status [22]. Obsessive-compulsive disorder (OCD) is a disorder of unknown etiology which consists of obsessions and compulsions. Obsessions (obsessive thoughts) involve unwanted, repetitive thoughts revolving around themes such as contamination mental images of violence and horrific scenes, or urges such as using a knife against another individual. Compulsions (obsessive actions) are repetitive behaviors such as washing, checking, counting, slow word repetition or religious rituals like worship that a person feels the urge to perform in order to respond to the obsessive thought or according to strict rules [23]. This disorder begins in childhood or adolescence and because of its chronic and severe nature it causes disability and distress in social and occupational activities and generally decreases the quality of life [24, 25]. Pharmacotherapy consists of three types of drugs: 1) selective serotonin reuptake inhibitors (SSRIs) that form the first line of treatment; 2) tricyclic antidepressants (TCAs), including clomipramine; and 3) serotonin-norepinephrine reuptake inhibitors (SNRIs), including venlafaxine. Sometimes antipsychotics are used alongside those drugs if the patient does not respond to treatment [26]. Patients are considered to be resistant to treatment if they are not adequately treated with SSRIs with a tolerable maximum dose for at least 3 months [27]. Free radicals and antioxidant defense system disorders result in pathogenic effects on human neural tissues; hence they are known to be important factors in the development of various brain disorders [28-32]. OCD may be associated with free radicals [33, 34]. In a study conducted by Ozdemir, it was found that serum levels of selenium in OCD patients were lower compared to healthy subjects [35]. However, the role of selenium in OCD has not been identified thus far. The aim of this study is to

determine if selenium use along with SSRIs can be effective in treating treatment-resistant obsessive-compulsive disorder.

## MATERIALS AND METHODS

### Study design

This study was a pilot randomized, double-blind, placebo-controlled clinical trial with a duration of 6 weeks and was conducted in accordance with the Declaration of Helsinki and subsequent revision [36]. This study was approved by the Ethics Committee of Jundishapur University of Medical Sciences, Ahvaz, Iran, IR.AJUMS.REC.1396.930 and Iranian Registry of Clinical Trials, IRCT20180212038699N. This clinical trial was conducted at the Outpatient Psychiatric Clinic of Imam Khomeini Hospital and the Bardia Private Psychiatric Clinic, both in Ahvaz, Iran, from February to April 2018.

### Patient Registration

The Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score was used to assess obsessive-compulsive disorder severity. This rating scale contains 10 items – the first 5 questions pertain to obsessive thoughts while the last 5 questions pertain to compulsive behaviors. Based on the severity of symptoms, the final outcome of the questionnaire is classified into one of five categories, ranging from subclinical to extreme OCD. The overall range of scores is from 0 to 40, with higher scores indicating greater OCD severity. The minimum score for this questionnaire was 21 for treatment-resistant patients [37]. At the time of entering the study, patients were evaluated by an interview for inclusion criteria and absence of exclusion criteria.

### Inclusion criteria

1) Patients diagnosed with obsessive-compulsive disorder according to DSM-V diagnostic criteria; 2) obsessive-compulsive disorder that is resistant to treatment for at least three months with SSRIs used at a maximum tolerated dose, and a Y-BOCS score of at least 21; 3) age between 18

and 62 years old; 4) absence of other psychiatric disorders, such as generalized anxiety disorder, panic disorder, major depressive disorder, and bipolar disorder; 5) absence of physical illness, such as diabetes, hypertension, hyperhidrosis and hypothyroidism; 6) normal lab test results, including complete blood count, liver and kidney function tests; ; 7) no alcohol or drug addiction; 8) signing the consent form; 9) not having suicidal thoughts; and 10) non-use of psychiatric medications (other than the ones administered during the trial) or psychotherapy during the study period.

### Exclusion criteria

1) Pregnant and lactating women or those who intend to become pregnant during the study; 2) IQ score less than 80; 3) patient unwillingness to continue treatment; and 4) an incidence of complications that make treatment impossible.

Out of 54 patients, 53 agreed to participate in the study and after being interviewed and evaluated for inclusion and exclusion criteria, 32 patients remained and were subsequently randomly divided into two equal groups in the one-to-one ratios using the random numbers table. Sixteen patients were allocated to the intervention group and the other 16 to the control group. Information about randomization was kept by someone who was not involved in the study. A CONSORT diagram of participants is shown in Figure 1.

### Intervention

Each patient in the intervention group received a total of 200 mcg of selenium capsules (made by Century, USA) while each patient in the control group received one placebo capsule similar to selenium (made by the Pharmaceutical Technology Development Center of the Ahvaz Jundishapur University of Medical Sciences) daily for 6 weeks. In addition, patients in both groups continued to use the SSRIs in the same dosage that were started at least 3 months prior. The results of the study were evaluated by comparing the Y-BOCS scores of patients at the time of entering and at the end of the sixth week. There was a response rate to treatment if a decrease of at least 25% was observed at the end of

the study [38]. Patients, in addition to presenting at the beginning and end of the study, were also seen at 2 and 4 weeks in order to check for side effects, discontinuing the study if any exclusion criteria developed.

**Statistical analysis**

Qualitative variables are expressed as frequency and quantitative variables as mean ( $\pm$ SD). Due to the small size of the sample, at first, the normality of the data distribution was calculated using the Kolmogorov-Simonov test and it was confirmed. Our independent variables included the type of intervention, age, sex, and marital status, whose effect on the dependent vari-

able (Y-BOCS) was measured. First, the demographic data of patients, including age, sex, and marital status, were compared between the two groups. The chi-square test was used to compare sex and marital status while the independent-samples t – test was used to compare age. Second, a comparison was performed between the Y-BOCS scores at the time of entering the study and at the end of the study by means of the paired-samples t-test and the results of these tests in both groups were considered statistically significant as  $P < 0.05$ . For a comparison between the type of SSRI used and the side effects observed in the two groups, Fisher’s exact test was used, and its significance was considered as  $P > 0.99$ . All analysis tests were performed using SPSS (version 22) statistical software.

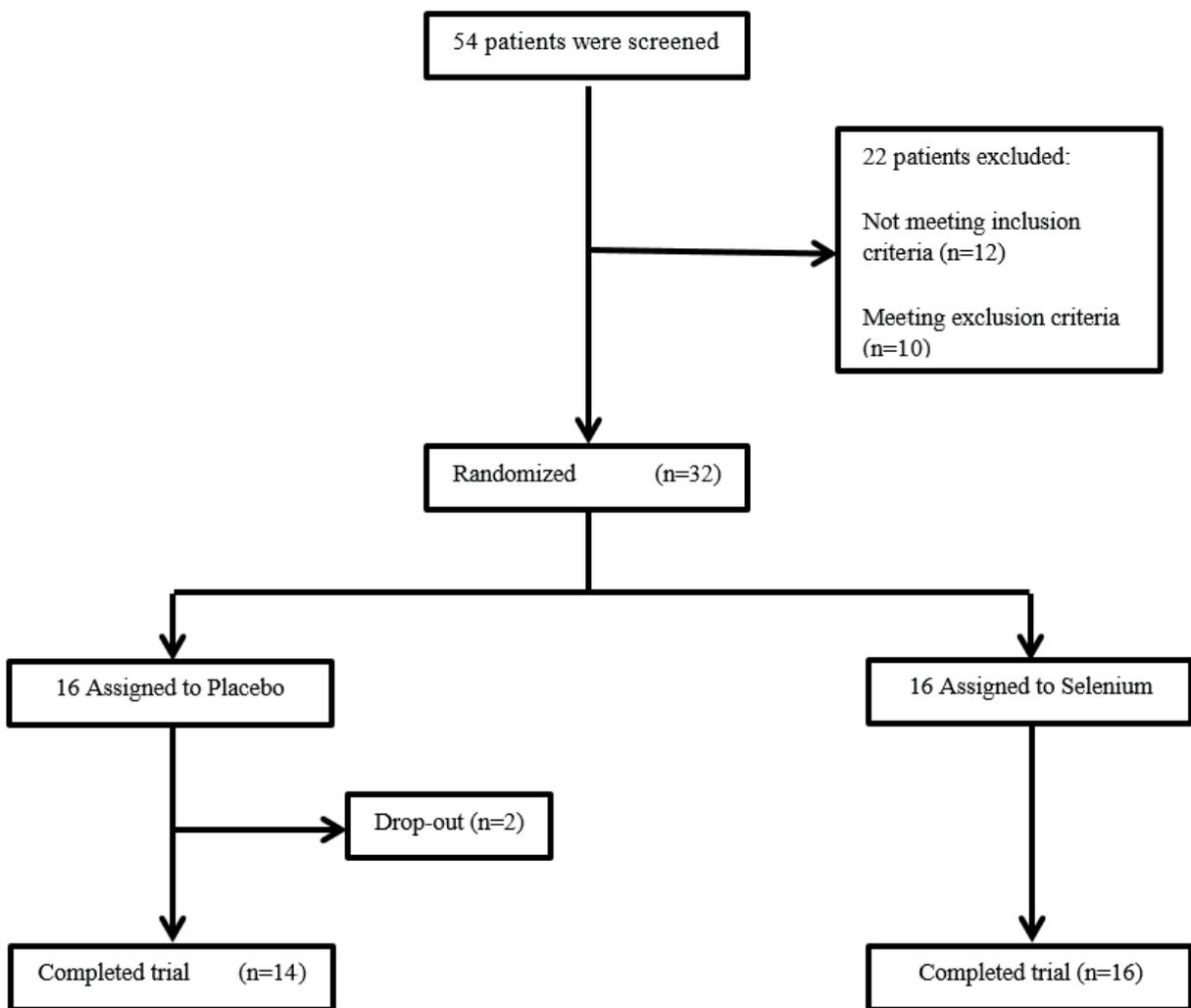


Figure 1. CONSORT diagram of participants

## RESULTS

### Demographic information and abrasion

Among the 32 patients enrolled in the study, 16 patients were in the selenium group and 16 in the placebo group. Unfortunately, two of the patients from the placebo group were excluded during the

study due to their unwillingness to continue treatment, and as a result, 14 patients remained in this group (see Figure 1). There was no significant difference between the two groups in demographic data (see Table 1). There was no significant difference in the type of SSRI used during the study between the two groups; the type and daily dose of SSRI used by patients have been shown in Table 2.

**Table 1.** Demographic data of the participants

Characteristic	Placebo group	Selenium group	<i>P</i>
Patients entered	16	16	
Patients evaluable	14	16	
Gender			
Female	9	5	Ns
Male	5	6	
Material status			
Married	6	6	Ns
Single	8	10	
Age (years)	Mean (SD)	Mean (SD)	Ns
	32.50±7.43	35.38±11.65	

Ns: not statistically significant.

**Table 2.** SSRI type dose range in Selenium and Placebo group

SSRI	Dose	Selenium	Placebo
(Type)	(Mg/day)	(n = 16)	(n = 14)
Sertraline	150-200	5 (31.2%)	4 (28.5%)
Paroxetine	40-60	4 (25%)	4 (28.5%)
Fluoxetine	70-80	3 (18.7%)	2 (14.2%)
Fluvoxamine	200-300	2 (12.5%)	2 (14.2%)
Citalopram	60-80	2 (12.5%)	2 (14.2%)

*Effect of treatment on Y-BOCS scores*

### Effect of treatment on Y-BOCS scores

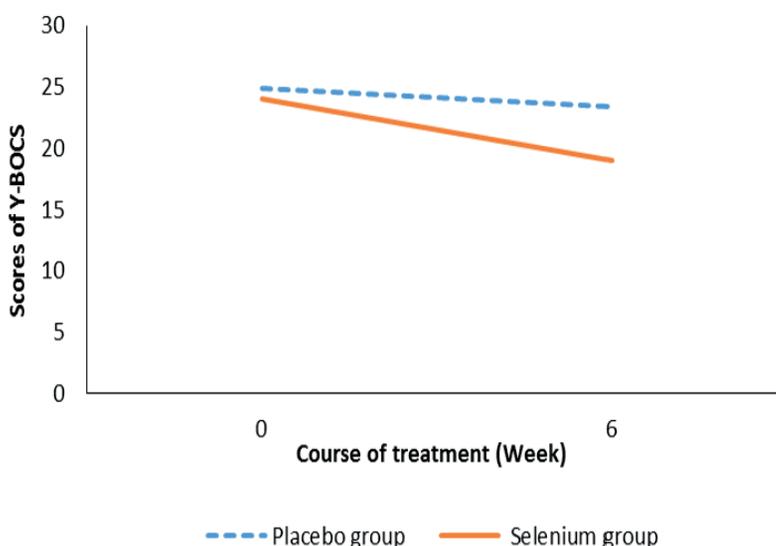
The mean score of Y-BOCS at the time of entry was 24.06 in the selenium group (SD = ± 3.4) and in the placebo group, it was 24.93 (SD = ± 4.2), with no significant difference ( $P = 0.64$ ). At the end of the sixth week, the mean values were 18.94 (SD = ± 5.2) in the selenium group and 23.36 (SD = ± 3.4) in the placebo group, with a statistically significant difference between the two groups ( $P = 0.01$ ). The changes

in Y-BOCS scores in both groups before and after the study is presented in Table 3. As shown in Figure 2, although the mean Y-BOCS value decreased in both groups after 6 weeks, this decrease was more pronounced in the selenium group. The results of this study demonstrated that Y-BOCS scores in the selenium group reduced by 21.2%. Upon further examination, it was noted that 7 patients from the selenium group (43.7%) and one patient from the placebo group (7.1%) had a decrease of at

least 25% in the Y-BOCS score, indicating a re-  
sponse to treatment.

**Table 3.** Clinical changes in Y-BOCS scores of patients receiving selenium (n = 16) versus placebo (n = 14) at baseline and after week 6

	Selenium (n=16)		Placebo (n=14)		Paired-samples t-test	
	Baseline Mean (SD)	End point Mean (SD)	Baseline Mean (SD)	End point Mean (SD)	Difference at baseline	Difference at end point
Y-BOCS score (obsessions)	12.56 (±2.5)	9.38 (±2.1)	12.93 (±2.8)	11.43 (±2.8)	<i>P</i> = 0.71	<i>P</i> = 0.02
Y-BOCS score (compulsions)	11.50 (±2.8)	9.56 (±2.7)	12.00 (±2.1)	11.93 (±2.2)	<i>P</i> = 0.53	<i>P</i> = 0.03
Y-BOCS (total score)	24.06 (± 3.4)	18.94 (± 5.2)	24.93 (± 4.2)	23.36 (± 3.4)	<i>P</i> = 0.64	<i>P</i> = 0.01



**Figure 2.** Effect of selenium and placebo on the Y-BOCS

**Table 4.** Reported adverse effects

Side effect	Placebo group (n = 14)	Selenium group (n = 16)	<i>P</i>
Sedation	2	3	Ns
Constipation	1	1	Ns
Decreased appetite	1	0	Ns
Nausea	0	1	Ns
Tremor	0	1	Ns
Sexual dysfunction	3	2	Ns

*Side effects*

Selenium was well tolerated and the side effects reported were mainly mild and transient. About 6 complications were reported and recorded, al-

though according to their profiles, it seems that most of these side effects were complications of SSRIs because, during the study, patients also received a high dose of SSRIs and observation of such complications was not beyond expecta-

tion. Nonetheless, these complications were recorded and statistically analyzed. There was no significant difference between the two groups in terms of side effects. Side effects that were reported are shown in Table 4.

## DISCUSSION

About 40-60% of obsessive-compulsive disorder patients do not respond adequately to SSRIs [39]. Treatment augmentation involves adding a drug with a different mechanism of action than the main drug used in order to increase therapeutic efficacy [40]. The results of this study indicate that selenium supplementation as an adjunct therapy can be helpful in obsessive-compulsive disorder patients who are resistant to first-line drugs and psychotherapy, and significantly reduces the symptoms of obsessive-compulsive disorder. Since selenium is a dietary supplement and has no intolerable side effects, as do other psychiatric drugs, good patient compliance was observed. The mechanism by which selenium acts to affect OCD is unknown, but studies have revealed that selenium in the body can regulate the level of some neurotransmitters, especially dopamine, and increase their turnover [41, 42]. Dopamine has been shown to be involved in the pathophysiology of OCD, which is why many patients respond positively to antipsychotics [43, 44]. There are several hypotheses that express the role of selenium in the synthesis and activity of thyroid hormones and thyroid protection from oxidative stress. In fact, the thyroid gland has the highest selenium content compared to any other tissue [45, 46]. Many of the enzymes containing selenoprotein, such as the three forms of glutathione reductase, 5-deiodinase type 1, thioredoxin reductase, and selenoprotein P, are functionally expressed in the thyroid, and control the metabolism of thyroid hormones in which the T4 prohormone is converted to the active T3 or the inactive rT3 isomer. On the other hand, there is a relationship between thyroid function and mood, so the effect of selenium on thyroid function can be the cause of the positive effect of selenium on the improvement of obsessive-compulsive disorder [22]. According to information from previous studies, this study is the first clinical trial in

the world that recommends the use of selenium supplementation in treatment-resistant obsessive-compulsive disorder. In order to be able to accurately state the results of this study, more studies will be necessary in this area.

## Limitations

This study had limitations such as a small sample size (30 patients), 2 patients out of the placebo group were excluded during the study, and the duration of the study was short (6 weeks). If Y-BOCS scores had been collected and recorded periodically during the study, not just at the beginning and at the end, it could have helped determine the exact timing of selenium's effectiveness. One of the most important limitations of this study was the level of selenium in the body of the patients, which may vary depending on the type of nutrition of the subjects and, consequently, affect the outcome of the study. In order to state that selenium is effective in the treatment of treatment-resistant OCD, the ideal reduction in the Y-BOCS score is at least 25%, which we did not achieve in this study with 100% of patients. However, it seems that if the study lasts longer or higher selenium doses are used, then perhaps better and more reliable results could be achieved.

## Acknowledgements

*In the end, we thank the patients who trusted us and participated in this study, as well as the staff of the Outpatient Psychiatric Clinic of Imam Khomeini Hospital and the Bardia Private Psychiatric Clinic for their collaboration on this study.*

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