Original Article

The Effect of Atorvastatin on Obsessive-compulsive Symptoms of Refractory Obsessive-compulsive Disorder (Add-on Therapy)

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Abstract

Background: Considering the effect of statins on the regulation of dopamine neurotransmitters and glutamates and importance of the treatment of obsessive-compulsive disorder (OCD) due to its relatively high prevalence and disability of available drugs in treatment of many patients, we came to the point to examine effectiveness of statins in patients with OCD. **Materials and Methods:** This study is a double-blind randomized clinical trial, which is done in OCD clinic of Isfahan Shariati in 2014 for 1 year. The target population consists of 64 patients with OCD; one group is given a daily 40 mg atorvastatin tablets and the other group receives placebo. At baseline, 4- and 8-week severities of obsessive-compulsive symptoms are measured using Yale–Brown scale and compared in the two groups. **Results:** The study results show a statistically significant difference between the two groups of intervention and control ($P < 0.001$). Furthermore, the results show the intervention effect at the end of the 4th week and 8th week ($P < 0.001$) that this change is evident in the 4th week but remained almost constant in the 8th week. **Conclusion:** Overall, the evidences obtained from the study declare the effects of adding statins to treat obsessive-compulsive symptoms.

Keywords: *Add-on therapy, atorvastatin, obsessive-compulsive disorder, refractory obsessive-compulsive disorder*

Introduction

Obsessive-compulsive disorder (OCD) has a prevalence of 2–3% of the general population and in patients referred to psychiatry clinics up to 10%.[1] OCD symptoms are very versatile and range from penetrating thoughts and obsessive preoccupation to the obsessive practices and customs.[2] Although 5-hydroxytryptamine (5-HT) is still known as major neurotransmitter involved in OCD symptoms, 5-HT abnormalities may be the result of OCD rather than the cause of it.[3] Among the treatments based on numerous published trials and according to several meta-analyses and practical guides, selective serotonin reuptake inhibitors (SSRIs) and clomipramine, which is also a serotonin reuptake inhibitor, are introduced as first-line treatment for OCD.[4-9]

The results from clinical and preclinical trials suggest that the dopamine system may be involved in the pathogenesis of OCD,[10] and it is proposed as the reduction of phase 1 in stimulation of D1 receptor in obsessive patients.[11] Despite the limited number of studies, the results of further research imply a link between OCD and increase of dopamine neurotransmission in the brain, and the hypothesis of an increase in dopamine neurotransmitter in the basal ganglia is agreed.[12] Furthermore, growing evidence supports the role of basal ganglia dopaminergic neurotransmission and midbrain that decrease the ability of frontal cortex to suppress emotional responses made in the amygdale.[10] Another neurotransmitter involved in the etiology of OCD is glutamate. In recent years, several lines of evidence have emphasized glutamatergic dysfunction in brain's corticostriatal thalamic-cortical circuitry in the etiology of OCD.[13] The importance of glutamate in the pathophysiology of OCD is proven and that causes the use of effective drugs on glutamatergic system in addition to the serotonergic drugs.[14,15] That's why the glutamatergic factors are new candidates in the treatment of OCD.[15,16]

Studies have shown that about 40% of patients with OCD do not respond to

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SSRI.[17,18] Search for second-line treatment strategies is clinically important in patients with OCD because patients with OCD are less responsive to treatment than other anxiety disorders, and probability of spontaneous recovery is low in OCD; therefore, there is a need for effective drug treatments to reduce long-term disability in such patients.[19,20]

Statins are drugs that their main function is to lower cholesterol and have anti-inflammatory and neuroprotective effects.[21] Several studies indicate statins' regulatory role on neurotransmitter dopamine in the striatum and its decrease in the prefrontal cortex.[21] Another study shows that simvastatin increases dopamine receptors in the prefrontal cortex of rats. High doses of simvastatin cause upregulation in D1 and D2 receptors expression in the prefrontal cortex with potential mechanisms of endothelial nitric oxide synthase. The results of this study suggest that statins can alter dopaminergic activity by probable central mechanism.[22] Studies have shown that statins are effective in regulating neurotransmitter glutamate. In one study, simvastatin reduced anxiety-like activity by maintaining the receptor expressions of N-methyl-D-aspartate (NMDA) in an experimental model of parkinsonism. NMDA receptor regulation by simvastatin partly explains the anxiolytic activity and its anti-inflammatory mechanisms in experimental models of parkinsonism. This study shows that statins can prevent neuronal degeneration of dopamine in experimental models of parkinsonism.[23]

High doses of simvastatin cause upregulation in NMDA receptors in different areas of the brain and can have hyperlocomotive and anxiolytic effects. Simvastatin plays an important role in the regulation of psycho-degenerative disorders by affecting NMDA receptors.[23] Although there were no particular clinical trials regarding the effectiveness of statins in obsession and given the importance of treating the OCD symptoms or attention to the positive effects of statins in preserving the function of brain neurons as well as the brain neurotransmitters and also the mechanisms of their effectiveness in other inflammatory based disorders and considering the safety of statins and no major negative effects, doing clinical trials to evaluate their effectiveness in OCD has a reasonable justification.

Materials and Methods

Study design and participants

The present study is a double-blind clinical trial, which assessed psychologist without the knowledge of the people are in which group evaluated the patients, patients without knowing which group they are in, were delivered their medication from the drug delivery person, in the meantime, delivery drug did not have aware about drugs (which one is drug and which one is placebo). IRCT2016041527392 and ethical university code 293116.

$n=\frac{2\left(Z_1\right)^2 S^2}{d^2}$, Z_1: Confidence coefficient = 0.095 it means 1.96, d: sampling error = 2 (minimum of OCD mean differences between two groups that reject zero hypothesis), and s: Maximum standard deviation (SD) for obsession = 1/6.

Using sample size formula, 64 patients with refractory OCD referring to obsession clinic of Shariati Isfahan in 2014 for 1 year are selected, regarding inclusion and exclusion criteria. They are randomly categorized into two groups (intervention and placebo). The study group of 64 patients with refractory OCD who are treated for at least 12 weeks with SSRI or clomipramine with the maximum tolerated dose and psychotherapy, and their scores on the scale of Yale–Brown are more than 16.[24]

Inclusion criteria include the presence of OCD criteria according to Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision, receipt of serotonergic drugs (SSRI or clomipramine) at least 12 weeks at the maximum tolerated dose, moderate to severe symptoms based on Yale–Brown Obsessive Compulsive Scale (Y-BOCS) score >16 [Figure 1], obtaining informed consent from patients, aged between 18 and 50 years, absence of mental retardation and disability, absence of serious medical conditions (chronic heart disease, lung disease, and diabetes), substance abuse, and pregnancy. Exclusion criteria include hypersensitivity to statins, high liver enzymes, refusal to complete the study, and planned pregnancy during the study. Sampling is random, and patients with inclusion criteria are in Group 1 (drugs) and Group 2 (placebo). Patients are divided into two groups according to the table of random numbers; raters, researchers and patients are not aware of the division of patients into the case and placebo groups. First, for ethical violations, investigators explain the steps, purpose, and duration to the participants, and consent forms are filled.

For intervention group, 20 mg atorvastatin is started a day till 1 month after the 1st month, based on patient's tolerance, the dose is increased 10 mg till it reaches 40 mg/day. The dose is determined on the basis of administration of

Y-BOCS TOTAL(add items 1-10) ☐ Date: Day / Mth. / Year / Rater

Patient Name | **Patient id**

	Obsessions	None 0	Mild 1	Moderate 2	Severe 3	Extreme 4
1	TIME SPENT ON OBSESSIONS	☐	☐	☐	☐	☐
1b	Obsession-free interval (do not add to subtotal or total score)	☐	☐	☐	☐	☐
2	INTERFERERENCE FROM OBSESSIONS	☐	☐	☐	☐	☐
3	DISTRESS OF OBSESSIONS	☐	☐	☐	☐	☐
4	RESISTANCE	☐	☐	☐	☐	☐
5	CONTROL OVER OBSESSIONS	☐	☐	☐	☐	☐
	OBSESSION SUBTOTAL(add items 1-5)	☐				

	Compulsions	None 0	Mild 1	Moderate 2	Severe 3	Extreme 4
6	TIME SPENT ON COMPULSIONS	☐	☐	☐	☐	☐
6b	Compulsion-free interval (do not add to subtotal or total score)	☐	☐	☐	☐	☐
7	INTERFERENCE FROM COMPULSION	☐	☐	☐	☐	☐
8	DISTRESS FROM COMPULSIONS	☐	☐	☐	☐	☐
9	RESISTANCE	☐	☐	☐	☐	☐
10	CONTROL OVER COMPULSIONS	☐	☐	☐	☐	☐
	COMPULSION SUBTOTAL(add items 6-10)	☐				

Figure 1. Yale–Brown Obsessive Compulsive Scale (Y-BOCS)

atorvastatin in patients with hypercholesterolemia.[14] The Group 2 receives placebo pills. In both groups, the previous dose of SSRI drugs or clomipramine that patients used to receive is maintained. Again, by the same psychologist, Y-BOCS is completed at the end of week 4 and 8.

A checklist of the effects of atorvastatin is prepared by the investigators, which includes the most common side effects of statins, headache, abdominal pain, and constipation. Another complication is myopathy and myalgia which happens in utmost 10% of consumers. An increase of liver enzymes in 1%–1.5% of patients who consume statins can be seen that if aspartate aminotransferase ≥3 goes up, atorvastatin is discontinued and otherwise it is continued. Initially, seventy patients enrolled in the study which three of them were excluded from the study after 1st month of using drug, due to drug reactions and not willing to continue. Three patients in placebo group left the study. Finally, 32 patients in each group complete the study. The researchers at all stages are committed to the provisions of the Code of Ethics and Ethics Committee of the Ministry of Health, Isfahan University of Medical Sciences. Written consent is taken from patients.

Collected data are analyzed by computer using SPSS software version 22 (SPSS Inc. Chicago, IlL) and statistical tests such as Friedman test and Mann–Whitney U-test for difference between groups (intervention and placebo). Friedman test used for follow-up time (trend of outcome while intervention). Normality of outcome has been checked by Shapiro–Wilk test. $P < 0.05$ is considered meaningful.

Results

In this project, 64 patients with OCD selected with age average 18–50. The majority of patients was women and divided into two groups randomly (intervention and placebo).

Shapiro–Wilk test showed that the OCD score was not normality distribution; because of this reason, we used nonparametric tests such as Friedman test and Mann–Whitney U-test.

The data showed the mean age of 36.2 and SD of 10.4 in the intervention group and mean age of 33.85 and SD of 9.8 in placebo group that 85% of them are female. More details are given in Table 1.

As shown in Table 1, Friedman test in both groups shows (intervention and placebo) a significant different during 8 weeks ($P < 0.001$).

From Table 2, data has shown that Y-BOCS score in baseline and the 4th week is significant and reduce in both groups ($P < 0.027$) as well as the difference between 4th week and 8th week ($P < 0.091$), but this reduction in treatment group is more than placebo group, whereas there is not significantly reduction between baseline and 8th weeks in both groups ($P > 0.219$).

Table 1: Mean and standard deviation and Friedman test, Yale-Brown score before the intervention, the 4th and 8th weeks of intervention and placebo groups

Variable	*n*	Mean (SD)	*P**
Intervention group			
Baseline	33	22.24 (5.02)	<0.001
After 4 weeks	30	16.86 (5.88)	
After 8 weeks	29	16.27 (7.31)	
Placebo group			
Baseline	30	23.56 (6.22)	<0.001
After 4 weeks	27	21.25 (8.33)	
After 8 weeks	26	18.88 (8.81)	

*Friedman test. SD: Standard deviation

Discussion

The aim of this study was to evaluate the efficacy of adding atorvastatin to the treatment of patients with refectory OCD.

Data show that Y-BOCS score in baseline and the 4th week is significant reduce in both groups ($P < 0.027$) and difference between 4th week and 8th week ($P < 0.091$), but this reduction in treatment group is more than placebo group, whereas there is not significantly reduction between baseline and 8th weeks in both groups ($P > 0.219$). Overall, the evidence obtained from the study represents the effects of adding statins to treat obsessive-compulsive symptoms.

Atorvastatin works by reducing the production of low-density lipoprotein (LDL) cholesterol by the liver. This has a knock-on effect of making the liver cells that take up LDL cholesterol from the blood. Atorvastatin also causes a small decrease in the production of other "bad fats" in the blood called triglycerides and a small increase in the level of high-density lipoprotein cholesterol. The overall result is lowered levels of "bad fats" and raised levels of "good fats" in the blood. Statins such as atorvastatin have an important role in the prevention of coronary heart disease and stroke because they reduce the risk of excess cholesterol being deposited in the major blood vessels of the heart and brain. Any blockage in these blood vessels limits the amount of blood and therefore oxygen that can be carried to the heart or brain. In the heart, this can cause chest pain (angina) and in severe cases can result in a heart attack (myocardial infarction), while in the brain, it can cause a stroke. Atorvastatin slows down hardening of the arteries, regardless of your initial cholesterol level. It reduces the risk of needing procedures to improve blood supply to the heart, such as a balloon dilation of an artery or a heart bypass graft. It also reduces the risk of heart attack, stroke, and death from heart disease.[21]

According to some studies, anti-inflammatory effects and neuroprotective of statins on preserving the function of neurotransmitters in the pathogenesis of OCD are confirmed.[20,25-29]

Table 2: Mann-Whitney test of the impact of intervention on obsessive-compulsive disorder symptoms in baseline, the end of the 4th week, and 8th weeks

Variant	Treatment group		Placebo group		*P**
	Mean (SD)	Median	Mean (SD)	Median	
Difference between baseline and 4th week	5.37 (5.5)	6	2.32 (5.5)	0	0.027
Difference between baseline and 8th week	5.96 (7.28)	8	4.68 (6.05)	3	0.219
Difference between 4th week and 8th week	0.59 (4.63)	0	2.26 (3.4)	2.3	0.091

*Mann–Whitney test. SD: Standard deviation

One of these effective neurotransmitters is dopaminergic system.[10] For this reason, in OCD patients, dopamine antagonists are suitable for augmentation.[30] Statins regulate neurotransmitter dopamine in the striatum and decrease dopamine in the prefrontal cortex.[22]

The mechanism of action of statins in OCD may be due to their pharmacological effects on 5-HT transporters and norepinephrine transporters in addition to dopamine.[30] On the other hand, glutamate is involved in the pathophysiology of OCD,[19,20] and it is found that statins are effective in the regulation of glutamate neurotransmitter.[23]

Among other immunological involvement in OCD is the increasing prevalence of OCD in patients with rheumatic fever and an increase in OCD-related disorders among relatives of patients with rheumatic fever. Tumor necrosis factor alpha (TNF-α) is an inflammatory cytokine in rheumatic fever and autoimmune disease. TNF-α polymorphism is associated with rheumatic fever, considering connection between rheumatic fever and OCD, the relation between OCD and TNF arises.[31] Previous studies have also shown that there is a close relationship between OCD and Tourette syndrome. Half of the patients with Tourette disorder have OCD criteria, and <10% of patients with OCD have Tourette syndrome criteria.[32]

In a study, it was shown that interleukin (IL)-12 and TNF concentration is increased in Tourette patients, and both of these markers increase in the later periods of exacerbation of symptoms. This study showed that exacerbation of symptoms associated with an inflammatory process is happened due synthesis of local and systemic cytokines that may affect the central nervous system.[33]

In a study of cytokines in Tourette disorder in children and adolescents, only those patients who had OCD at the same time showed significantly increased levels of IL-12. In this group, IL-2 was significantly higher than other groups. This study indicated that OCD associated with Tourette disorder is effective on cytokine profile.[34] Statins reduce the secretion of IL-6 caused by lipopolysaccharide.[35] Statins are related with inflammatory cytokines, and patients with statin treatment have lower C-reactive protein levels.[36] In a study, it is reported that statins exert their anti-inflammatory effects in endothelium and leukocytes through downregulation cytokines. In this study, reduction of IL-6 and IL-8 followed by statin therapy is observed.[37] The above evidence indicates that statins can reduce the symptoms of OCD through the reduction of inflammatory factors. Statins can also cause oxidative stress reduction. In another study, statins reduced oxidative stress in patients with chronic obstructive pulmonary disease and ischemic heart disease.[38,39] Therefore, statins can stop pathophysiology of oxidative stress causing OCD.

Conclusion

All the above evidence suggests that statins can reduce OCD symptoms by various mechanisms. Hence, these drugs can be considered as adjuvant in the treatment of obsessive-compulsive disorder.

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Conflicts of interest

There are no conflicts of interest.

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