Effects of atorvastatin on treatment-resistant obsessive-compulsive disorder: A double-blind randomized trial

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Summary

Objective. Obsessive compulsive disorder (OCD) is a chronic disorder of unknown etiology. An augmentation strategy is an approach for treatment-resistant OCD. This study was planned to assess the effect of atorvastatin on treatment-resistant OCD.

Methods. This 12-week-long double-blind randomized trial was performed on 26 adult patients with treatment-resistant OCD. They were diagnosed with this kind of disorder based on the DSM-IV-TR. The patients were randomized to receive either 10 mg/day atorvastatin or placebo. The Yale–Brown scale was assessed at the baseline and 12 weeks later.

Results. There were significant reductions in the obsession subtotal score of the Y-BOCS (p = 0.017) and the total Y-BOCS score (p = 0.041) in the atorvastatin group. Hence, the reduction in the Y-BOCS compulsive score (p = 0.081) was not statistically significant. Atorvastatin was generally well tolerated. There was a significant reduction in libido in the atorvastatin group (p = 0.019).

Conclusions. The results of this study should be interpreted in the shadow of its restrictions. Some of the restrictions were a limited number of patients in the trial, a 12-week-long time trial, and not measuring NO before and after the study. It is recommended that researchers should consider these items in similar type of studies.

Keywords: Augmentation; treatment-resistant obsessive-compulsive disorder (OCD); Atorvastatin
Introduction

Obsessive-compulsive disorder (OCD) is a prolonged psychiatric disorder with a suggested life expectancy prevalence of 2%–3% in the general population. OCD patients may experience profound nervousness caused by unwelcome, intrusive, constant idea, images, or impulses (obsessions). These symptoms lead to recurrent behavior or mental acts (compulsions) and hence the patients feel driven to avert or decrease their distress or anxiety [1]. As many as 40%–60% of patients with OCD are resistant to current medication such as SSRI and clomipramine [2]. Pallanti and Quercioli [3] proposed a threshold of Y-BOCS score reduction for three conditions, namely full response (35% or more), partial response (25%–35%), and no response (less than 25%).

There are many strategies for treating OCD patients; these include augmentation with antipsychotic drugs (olanzapine, risperidone and haloperidol) [4–6] or mood stabilizer drugs such as valproate and lamotrigine [7]. The aim of treating OCD patients is to increase the responses and decrease the side effects of SSRI or clomipramine. One of the possible etiologies of OCD is post-inflammation and infection in the central nervous system (CNS) [8–10].

Nitric oxide (NO) is one of the important neurotransmitters, which is known to implicate in behaviors like learning, pain perception, aggression [11], depression [12], and anxiety [13]. NO also plays a role in the obsessive-compulsive behavior [14]. NO has been suggested to play a crucial role in several brain functions or dysfunctions including synaptic plasticity, depression, and the regulation of neuronal excitability [13]. NO may also play an important role in most brain areas related to defensive reactions, since nitric oxide synthase (NOS)-positive neurons are located in such areas [14]. On the other hand, NO may affect dopamine [15] and glutamate [16]. A modulatory role of NO on brain areas related to defensive reactions – through the possible interaction with glutamate, serotonin, and/or GABA-mediated neurotransmission – has been proposed previously [11]. During the last few decades, there has been marked improvement in the attention paid to the possibility of immune – and infection-mediated OCD and related disorders. The term Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) refers to a child who has been diagnosed with sudden OCD and/or tic disorders following a streptococcal infection [7]. Recent epidemiologic evidence has revealed that there is modest evidence for a possible association and familial co-aggregation between PANDAS and OCD [17, 18].

Atorvastatin is a selective competitive inhibitor of HMG-CoA reductase [17], which is usually used to treat high cholesterol. In recent evidence, atorvastatin has been reported to play an important role in endothelial NO syntheses [18], suppression of inflammation [19, 20], and increased glutathione and GABA levels in mice [21].

With the pathogenic role of NO and inflammation in OCD as well as the effects of atorvastatin on inflammation and NO, we have decided to evaluate effects of atorvastatin on the treatment of resistant OCD.
Material and method

Study design, setting, and population

The study was a prospective double-blind 12-week-long trial including two parallel groups of outpatients with resistant OCD in Imam Khomeini Hospital of Ahvaz, Iran. The patients were selected randomly and they participated in the study from November 2011 to July 2013. The authors screened all patients who were referred to psychiatric clinics as the definition of resistance for resistant OCD required three months of maximal monotherapy treatment with SSRIs [19, 20]. The subjects were randomized to the treatment arms in a 1:1 ratio. Patients with a clinical diagnosis of OCD were chosen according to the DSM-IV-TR criteria and the DSM diagnosis was done based on SCID. Those with a diagnosis of moderate-to-severe OCD were defined by the Yale–Brown obsessive compulsive scale (Y-BOCS) score of ≥ 21.

Inclusion criteria

Inclusion criteria were as follows: resistant OCD (a patient should undergo continuous monotherapy treatment with SSRIs for three months to be defined as resistant) and signing informed consent were required. Besides, a minimum score of 21 or higher in the Yale–Brown scale (Y-BOCS) for OCD was needed for inclusion in the study [22]. The patients did not have any organic neurological disorders, and laboratory tests for blood count and liver and renal functions were normal.

Exclusion criteria

Exclusion criteria were as follows: innate neurological disorders; abnormal laboratory test results for blood count liver and renal functions; breastfeeding; pregnant women.

Method

Two psychiatrists confirmed the diagnosis of OCD based on the DSM-IV-TR [22] and the resistant OCD based on the research of Goodman et al. [23] and Ferraro et al. [24]. Two general practitioners (GPs) were trained to establish the inter-rater reliability of Y-BOCS ratings, and the scores of each patient were obtained by them at the start and end of the treatment period. After considering the inclusion and exclusion criteria and obtaining written informed consents from the patients or their guardians, all the patients were interviewed face-to-face and the purpose of the study was explained to them.
Intervention

In the drug group, the patients were given 10 mg/day atorvastatin (Sobhan Pharmaceutical Company, Iran) and the response, which was measured with the Yale–Brown scale, was assessed at the baseline and on completion of the study 12 weeks later. In the placebo group, the patients received placebo that was manufactured to mimic atorvastatin and the same outcome was observed at baseline and on completion of the study 12 weeks later.

The rationale behind low-dose (10 mg/day) atorvastatin therapy for resistant OCD was to use the minimal effective dose in accordance with latest randomized clinical trials (RCTs) [25, 26] that compared high-dose atorvastatin (80 mg/day) with standard doses (10–40 mg/day).

Outcomes

The primary outcome includes changes in the Yale–Brown scale at the baseline and on completion of the study 12 weeks later. Secondary outcome measures were side-effects at the baseline and on completion of the study 12 weeks later.

Sample size

Among the 89 referred patients interviewed during this period, 48 patients confirmed the diagnosis of treatment-resistant OCD and 30 patients agreed to participate in the study. After informed consent letters were obtained, the patients entered the study. Eligible participants in the study were 26 patients with OCD whose age ranged from 24 to 48 years. None of the patients and MDs was informed about which group the patients had been assigned.

Randomization

Randomization was done using the random digit table.

Blinding

The placebo tablets, prepared by the Food and Drug Department of Ahvaz Jundishapur University of Medical Sciences, were composed of starch and were similar to atorvastatin tablets in size, shape, and color. The drug and placebo tablets were administered to patients by a staff member who was not privy to the treatment. The patients were also not privy to the treatments.
Ethical approval

The patients did not receive any other treatment, such as cognitive and behavior therapy, during the trial period. The trial was performed in accordance with the Declaration of Helsinki and subsequent revisions [22]; it was approved by Ethical Committee of Ahvaz Jundishapur University of Medical Sciences and registered at www.IRCT.ir with the reference code of IRCT201511217290N2. Written informed consents were obtained from the participants before the study.

Statistical analysis

Data was subjected to quality control and subsequently descriptive and inferential statistical analyses were performed. Continuous data was expressed as mean (SD). A comparison between the groups at the baseline and at the end of 12 weeks was drawn using the Mann-Whitney \( U \) test for two independent samples. In addition, an intention-to-treat analysis with the last observation carried forward (LOCF) was performed to ensure that drop-out does not produce any bias in the result. Non-continuous data was expressed as percentages, and the comparison between the two groups was performed by using the \( \chi^2 \) test. The frequency of treatment-induced adverse effects in the study groups was analyzed by Fisher’s exact test. All statistical tests were two-sided and considered statistically significant at \( p < 0.05 \). Treatment response was defined as a reduction of the Y-BOCS scores of \( \geq 25\% \) with respect to the baseline evaluation.

Results

As many as 29 patients were screened. Among them, 26 completed the trial and were included in the analysis of efficacy. In total, 14 patients were randomly assigned to the atorvastatin group and 12 to the placebo group. In this trial, three patients were dropped, including two patients in the placebo group and one in the atorvastatin group. The study groups were matched and showed no statistically significant differences with respect to demographic factors (Table 1). The treatment attrition did not differ between the two groups. All patients had been on SSRI therapy at the highest tolerable dose range (Table 2). These doses had been fixed at least three months in all patients before the study.

Table 1. Demographic data of the participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo group</th>
<th>Atorvastatin group</th>
<th>( p^1 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients entered</td>
<td>14</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Patients evaluable</td>
<td>12</td>
<td>14</td>
<td></td>
</tr>
</tbody>
</table>

\( ^1 \text{table continued on the next page} \)
Table 2. **SSRI type and dose range in atorvastatin and placebo groups**

<table>
<thead>
<tr>
<th>SSRI (Type)</th>
<th>Dose (mg per day)</th>
<th>Atorvastatin group N = 14</th>
<th>Placebo group N = 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>70–80</td>
<td>4 (28.6%)</td>
<td>3 (25%)</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>200–300</td>
<td>6 (43.8%)</td>
<td>6 (50%)</td>
</tr>
<tr>
<td>Sertraline</td>
<td>150–200</td>
<td>1 (6.1%)</td>
<td>1 (8.5%)</td>
</tr>
<tr>
<td>Citalopram</td>
<td>60–80</td>
<td>3 (21.5%)</td>
<td>2 (16.5%)</td>
</tr>
</tbody>
</table>

At the baseline, the two groups did not differ significantly in the Y-BOCS score (p = 0.957). At the endpoint, the total score of Y-BOCS in the atorvastatin group decreased significantly (p = 0.041) (Table 3). Atorvastatin augmentation significantly reduced obsessive and affective symptoms in accordance with changes in the Y-BOCS obsession subscale (p = 0.017), while the decrease in compulsion was not statistically significant (p = 0.081) (Table 3).

Table 3. **Clinical changes in Y-BOCS scores of patients receiving atorvastatin (n = 14) versus placebo (n = 12) at baseline and in 12th week**

<table>
<thead>
<tr>
<th>Y-BOCS</th>
<th>Atorvastatin (14)</th>
<th>Placebo (12)</th>
<th>Mann-Whitney U Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline Mean (SD)</td>
<td>Endpoint Mean (SD)</td>
<td>Baseline Mean (SD)</td>
</tr>
<tr>
<td>Obsession scores</td>
<td>13.26(3.2)</td>
<td>8.64(2.6)</td>
<td>12.42(5.1)</td>
</tr>
<tr>
<td>Compulsion scores</td>
<td>12.25(4.7)</td>
<td>11.21(3.1)</td>
<td>13.57(1.6)</td>
</tr>
<tr>
<td>Total scores</td>
<td>25.51(5.2)</td>
<td>19.85(5.2)</td>
<td>25.99(4.3)</td>
</tr>
</tbody>
</table>

We also found a gradual decline in mean Y-BOCS scores in both study groups during the trial. There was a significant effect of time (F = 34.8, df = 1.12; p = 0.22) and the treatment (F = 2.68, df = 1.45, p = 0.025). Likewise, time-by-treatment interaction was also significant (F = 3.7, df = 1.13, p = 0.041). Although three patients were dropped
Effects of atorvastatin on treatment-resistant obsessive-compulsive disorder

out from the research, intention-to-treat analysis (LOCF) showed significant decrease in Y-BOCS scores in the atorvastatin group (Table 4). With regard to the obsession sign, atorvastatin augmentation of SSRIs reduced scores by 34.8% in the atorvastatin group at the endpoint. This reduction showed that atorvastatin augmentation leads to a partial response to therapy in OCD patients.

Table 4. Intention to treat (LOCF): Clinical changes in Y-BOCS scores of patients receiving atorvastatin \((n = 15)\) versus placebo \((n = 14)\) at baseline and in 12th week

<table>
<thead>
<tr>
<th>Y-BOCS</th>
<th>Atorvastatin (15)</th>
<th>Placebo (14)</th>
<th>Mann-Whitney U Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline Mean(SD)</td>
<td>Endpoint Mean (SD)</td>
<td>Baseline Mean (SD)</td>
</tr>
<tr>
<td>Obsession scores</td>
<td>13.68(3.5)</td>
<td>8.82(2.3)</td>
<td>13.12(4.2)</td>
</tr>
<tr>
<td>Compulsion scores</td>
<td>12.81(3.6)</td>
<td>11.68(4.2)</td>
<td>14.12(1.9)</td>
</tr>
<tr>
<td>Total scores</td>
<td>26.49(5.4)</td>
<td>20.5(5.4)</td>
<td>27.24(4.9)</td>
</tr>
</tbody>
</table>

The final result showed that patients experience a 21.9% decrease in the mean Y-BOCS score in the atorvastatin group at the endpoint. Nine (64.2%) patients in the atorvastatin group had 25% or greater reduction in total Y-BOCS scores; they experienced a better feeling about the healing of their illness – especially with regard to the obsession sign. Atorvastatin was generally well tolerated. The effects were generally mild and transient. A common side effect was declining libido (35.7%) in the atorvastatin group \((p = 0.019)\) (Table 5).

Table 5. Clinical complications and side effects were reported as number per group

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Atorvastatin</th>
<th>Placebo</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restlessness</td>
<td>2</td>
<td>1</td>
<td>Ns</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1</td>
<td>1</td>
<td>Ns</td>
</tr>
<tr>
<td>Libido decrease</td>
<td>5</td>
<td>1</td>
<td>0.019</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>1</td>
<td>Ns</td>
</tr>
<tr>
<td>Palpitation</td>
<td>1</td>
<td>1</td>
<td>Ns</td>
</tr>
<tr>
<td>Sedation</td>
<td>1</td>
<td>2</td>
<td>Ns</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>1</td>
<td>Ns</td>
</tr>
</tbody>
</table>

Discussion

OCD is a common and chronic disability disorder with high costs for patients and their families. Diverse causes of the obsessive–compulsive disorder have been cited; these causes can be seen in case of the deregulation in the types of neurotransmitters
such as serotonin, dopamine, and so on, to a disturbance in the BG and inflammation. Studies have shown that infectious factors, such as PANDAS, are almost 10% causes of this disease [1, 25]. The aim of this study was to investigate the effect of atorvastatin on the symptoms of OCD in treatment-resistant patients. In this study, the treatment-resistant patients were given SSRIs and placebo or atorvastatin so that the atorvastatin group reported significantly fewer symptoms of the disorder at the end of 12th week. Also, no significant difference was found among the side effects in the two groups, except for decreased libido. Reduced libido in the atorvastatin group showed a greater reduction. The impact of this drug in patients indicates that NO and inflammation are among the important causes of the disease, and perhaps resistance to treatment in some patients with OCD is induced by the impact of these factors in the pathology of this disease.

The role of NO in OCD has been reported in several studies [14, 26]. One of the effects of SSRIs is its role in the inhibition of the synthesis of NO. Mechanisms such as inflammation, neurotransmitters of NO, dopamine, and glutamate have been mentioned as some causes of OCD. Since the prevalence of various treatment-resistant OCD is high, the use of new methods of pharmacotherapy to control the drug resistant should be appropriately justified by the possibility of influencing the less compulsive causes. For example, with regard to the inflammatory causes, a combination of celecoxib and SSRIs has been used [27]. We can help to treat these patients by using these methods and finding more decisive evidence in understanding the pathology of the disorder.

According to the results of this study, this theory can be suggested that drugs such as SSRIs and clomipramine are commonly used as first-line treatments for OCD. They are important factors in the treatment of OCD. This proves their influence mainly through the impact on the deregulation of serotonin. If the deregulation of serotonin is not the main factor of the disease in an OCD patient, it would be difficult to cure and the patient would be considered as treatment-resistant. And those patients who are influenced by other factors, such as deregulation of glutamate, NO, dopamine, or inflammation in the pathogenesis, are known as treatment-resistant patients. If therapists and researchers can find a strategy for understanding a more accurate etiology in every patient with an obsession and then proceed to the treatment based on that pathology, the number of the treatment-resistant patients will be less in future. Hence, the treatment gets faster and better, which makes it more efficient and increase the acceptance of patients and patients’ attitude to the psychiatric treatment gets better. Some methods for understanding the exact etiology of this disease are the preparation of a more accurate description, preparation of genealogy, the genetically exact check, the use of tests to measure neurotransmitters, and more accurate imaging.
Limitations

The limitations of this study, including the relatively small sample size and only a minimal dose of Atorvastatin, should be considered, and we offer some suggestions for future research.

Conclusions

The results of this study should be interpreted in the shadow of its restrictions. Some restrictions were a limited number of patients in the trial, a 12-week-long time-trial, and not measuring NO before and after the study. It is recommended that researchers should consider these items in this type of studies.

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References


21. Sehar N, Agarwal NB, Vohora D, Raisuddin S. Atorvastatin prevents development of kindling by modulating hippocampal levels of dopamine, glutamate, and GABA in mice. Epilepsy Behav. 2015; 42: 48–53.


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