

# The effect of atomoxetine on cognitive function in patients with multiple sclerosis

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## Keywords

Multiple Sclerosis; Cognitive Disorders; Atomoxetine Hydrochloride

## Abstract

**Background:** Recent research shows that most of the patients with multiple sclerosis (MS) have cognitive-like disorders. Due to the beneficial effects of atomoxetine on improving cognition in limited animal and human surveys, the aim of the present study was to investigate the effect of the atomoxetine on improving cognitive disorders of MS.

**Methods:** This study was a parallel, randomized clinical trial, designed to investigate the effect of atomoxetine drug on the improvement of cognitive impairment (CI) in MS, from April 2021 to March 2022. According to the inclusion and exclusion criteria, a total of 52 participants were involved in the study and then randomly divided in two groups of 26. Experimental group was treated with atomoxetine and the control group was treated with placebo. The Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS) test was performed for

assessment at the beginning and after 3 months. The California Verbal Learning Test (CVLT), the CVLT-delay, the Brief Visuospatial Memory Test-Revised (BVMT-R), and the Symbol Digit Modalities Test (SDMT) were used to evaluate the CI and changes following medication. Finally, data were analyzed by SPSS software at significance level of 0.05.

**Results:** The mean age of patients in the experimental group was  $37.7 \pm 8.5$  and in the placebo group was  $37.8 \pm 7.6$  ( $P = 0.32$ ). The results showed significant changes in cognitive levels before and after the use of atomoxetine and also in comparison to the placebo group ( $P < 0.05$ ).

**Conclusion:** This study showed that atomoxetine improved the cognitive domains after administration compared to placebo.

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## Introduction

Multiple sclerosis (MS) is a chronic, autoimmune disease of the central nervous system (CNS) and the most common debilitating neurological disorder in young people, which is a combination of genetic, infectious, environmental, or autoimmune factors.<sup>1,2</sup> Women are approximately 2.5 times more likely to develop the disease.<sup>3</sup> Recent studies show that the disease has a deep impact on all aspects of patients' lives in up to 65% of patients in every phase of the disease and it is more common in men and older age, as well as in secondary progressive (SP) and primary progressive (PP) in comparison with relapsing-remitting (RR) type.<sup>4-10</sup>

The main factors affecting cognitive decline include psychiatric comorbidities, metabolic disorders, fatigue, emotional disorders, substance abuse, age, and quality of life (QOL).<sup>11</sup> The progression of cognitive impairment (CI) in MS is unpredictable and does not relate to the level of disability and disease duration.<sup>12</sup> The most common cognitive dysfunction in MS includes slowing of cognitive processing speed and episodic memory loss, and is associated with problems with executive function, verbal psychology, visual-spatial analysis, and word-finding. Cognitive decline often appears in early stages; it may be qualitatively different in people with progressive type in comparison with RR type.<sup>13-18</sup>

Cognitive tools developed for MS include tests of processing speed, memory, and other functions that were performed separately by trained professionals. They mentioned the Symbol Digit Modalities Test (SDMT) (the most sensitive), the Brief Visuospatial Memory Test-Revised (BVRT-R), and the California Verbal Learning Test-Second Edition (CVLT-II) as the most sensitive tools available for cognitive monitoring in patients with MS.<sup>19,20</sup>

Despite the high prevalence and deep impact on patients' lives, there are no approved medications for the treatment of CI in MS. Although various studies suggested several treatments and cognitive training to enhance cognition, there is no consensus on this. Data from several large-scale trials including interferons, fingolimod, and natalizumab have demonstrated beneficial effects in terms of delaying and perhaps improving cognitive function but so far, strongest benefit has been reported after cognitive training.<sup>21-23</sup>

Recently, atomoxetine (a norepinephrine reuptake inhibitor) has been suggested as a cholinergic drug, which helps to improve cognition and memory in rats.<sup>24,25</sup> A study of the

effects of atomoxetine on mice showed that the drug dose-dependently improved attention, impulsive behaviors, and spatial memory, as well as executive functions in adult mice and improved concentration in older monkeys.<sup>26</sup> Moreover, several studies showed the positive effect of atomoxetine on the cognition of patients with Parkinson's disease, especially executive function.<sup>27-31</sup>

Although drug treatments for reducing MS activity have expanded dramatically over the past years, there is no effective treatment for cognitive problems. Therefore, there is a need to find new strategies that can be used to prevent cognitive decline, especially in the early stages of MS.<sup>32</sup> Due to the beneficial effects of atomoxetine on improving cognition in limited animal and human studies, we aimed to investigate the effect of this drug on improving cognitive disorders in patients with MS.

The results of this study showed significant changes in the cognitive levels after taking atomoxetine compared to before medication, and also in the atomoxetine group compared to placebo group.

## Materials and Methods

**Study design:** The present study was a parallel, double blind, block randomized clinical trial designed to investigate the effect of atomoxetine on the improvement of CI in MS, based on the available facilities and time limit, from April 2020 to March 2021. According to inclusion and exclusion criteria, the eligible patients were assigned to each of the treatment groups.

**Randomization:** A total of 52 people were involved in a randomized, placebo-controlled, double-blind clinical trial (the patients and the researchers did not know placebo and atomoxetine group participants). First, the objectives of the study and the importance of its results were elucidated to the patients, then patients signed informed consent forms and entered the study. Next, the people were randomly designated into two groups of 26 people. This randomization was done with the help of the block randomization method. There were four people in each block; two people were assigned to the intervention group and two people were assigned to the control group. The arrangement of people in each block was random. Randomization was done using WinPepi software. The patients in the first group received atomoxetine and the second group received placebo.

### Inclusion criteria

1. Diagnosis of MS according to McDonald

criteria (all types)

2. Age between 18 to 55 years
3. Measurable CI based on the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS) test attributed to MS

#### Exclusion criteria

1. Using stimulant drugs
2. Clinical recurrence of MS within 60 days of screening
3. Change in the treatment of MS within 90 days of screening
4. Any underlying factor and disease that causes dementia and CI (uremia, liver disease, thyroid disease, vitamin B12 deficiency, and psychiatric disorder)
5. Proof of moderate to severe depression with Beck's Depression Inventory (BDI) (score  $\geq 9$ )
6. Contraindications to the use of atomoxetine: a history of suicidal ideation over the past year, diagnosis of bipolar disorder

**Intervention:** In group A, 26 patients were treated with atomoxetine at a dose of 40 mg daily for 2 weeks and then increased to 40 mg twice a day for 2.5 months. MACFIMS was performed again after 3 months. Group B consisted of 26 patients who were treated with placebo once a day and then increased to 40 mg twice a day for 2.5 months (like experimental group) and were followed for three months. At the beginning of treatment and end of third month, MACFIMS test was done. Since no medication has been approved by Food and Drug Administration (FDA) for the treatment of cognitive disorders, the group B was given only placebo.

**Outcome measurement:** At the beginning of the study, patients underwent MACFIMS test. The MACFIMS is composed of seven neuropsychological tests, covering five cognitive

domains commonly impaired in MS (processing speed/working memory, learning and memory, executive function, visual-spatial processing, and word retrieval). Group randomization was done by block randomization method using 4 blocks by WinPepi 11.4 software. In addition, in the present study, the CVLT (learning and memory), CVLT-delay, BVMT (delayed recall and recognition), and SDMT (processing speed/working memory) were used to evaluate the extent of CI. Then CI changes were measured before and after the intervention.

Data were analyzed by SPSS software (version 22, IBM Corporation, Armonk, NY, USA). In order to describe the data, mean and standard deviation (SD) or median and interquartile range (IQR) were used for continuous variables with normal and non-normal distribution, respectively; moreover, number and percentage were used for describing categorical data. For analytical analysis, Mann-Whitney U test and the Wilcoxon signed-rank test were used to test between- and within-group difference of cognitive function, respectively. Kolmogorov-Smirnov test was used for assessment of normal distribution of continuous data. The significance level of the tests was considered less than 0.05.

#### Results

A total of 52 patients were divided into two groups. 26 patients in the atomoxetine group were compared to 26 patients in the placebo group. The mean age of patients in the atomoxetine group was  $37.7 \pm 8.5$  and in the placebo group was  $37.8 \pm 7.6$  years. 37 participants were women; experimental group included 18 women (69.2%) and 8 men and the placebo group included 19 women (73%) and 7 men. Table 1 shows the demographic data in details.

**Table 1.** Demographic data of patients with multiple sclerosis (MS) participating in the study at baseline

Demographic data	Variable	Placebo [n (%)]	Atomoxetine [n (%)]	P
Gender	Women	19 (73.0)	18 (69.2)	0.70
	Men	7 (27.0)	8 (30.8)	
Type of MS	Relapsing-remitting	15 (57.7)	20 (76.9)	0.14
	Secondary-progressive	4 (15.4)	2 (7.7)	
	Primary-progressive	3 (11.2)	4 (15.4)	
	Progressive-relapsing	4 (15.4)	-	
Educational status	High school	6 (22.3)	2 (7.7)	0.20
	Diploma	3 (45.8)	6 (23.1)	
	Bachelor	11 (22.3)	12 (46.2)	
	Higher than a bachelor's degree	6 (9.6)	6 (23.1)	
Side effects	Nausea	1 (3.8)	4 (15.4)	-
	Insomnia	2 (7.7)	5 (19.2)	
	Dry mouth	-	2 (7.7)	
	Urinary retention	-	1 (3.8)	

MS: Multiple sclerosis

**Table 2.** Comparison of changes in cognitive tests

Variable	Group	Pretest	Posttest	P*	Change	P**
CVLT	Atomoxetine	40.23 ± 8.60	49.65 ± 11.80	0.001	9.42 ± 6.10	0.001
	Placebo	45.38 ± 12.80	47.92 ± 10.70	0.110	2.53 ± 7.00	
CVLT-delay	Atomoxetine	7.54 ± 3.10	10.35 ± 3.30	0.001	2.80 ± 2.40	0.001
	Placebo	11.27 ± 2.80	11.00 ± 3.30	0.580	-0.26 ± 2.40	
BVMT-delay	Atomoxetine	17.38 ± 6.80	23.12 ± 11.20	0.001	2.34 ± 2.80	0.001
	Placebo	18.23 ± 8.10	18.38 ± 8.40	0.640	-0.38 ± 1.20	
BVMT-total	Atomoxetine	5.73 ± 3.10	8.08 ± 3.90	0.001	5.73 ± 7.60	0.001
	Placebo	7.54 ± 3.90	7.15 ± 3.90	0.140	0.15 ± 1.60	
SDMT	Atomoxetine	27.54 ± 9.90	33.92 ± 11.80	0.001	6.38 ± 5.90	0.001
	Placebo	30.04 ± 15.00	29.88 ± 15.00	0.760	-0.15 ± 2.50	

Data are presented as mean ± standard deviation (SD)

\*Paired t-test; \*\*Independent t-test

BVMT: Brief Visuospatial Memory Test; CVLT: California Verbal Learning Test; SDMT: Symbol Digit Modalities Test

In the atomoxetine group, the minimum period of the disease was 1 year and the maximum period was 17 years with a mean of  $9.3 \pm 5.2$  years. In the placebo group, the minimum period of the disease was 1 year and the maximum period was 17 years with an average of  $9.5 \pm 6.3$  years. Among 12 patients, 23.1% showed complications. The results of this study showed significant changes in the cognitive levels after taking atomoxetine compared to before medication, and also in the atomoxetine group compared to placebo (Table 2). Medication uses and medication effects on cognitive disorders were compared with placebo group. CVLT, CVLT-delay, BVMT, and SDMT were used before and after the intervention. According to table 2, there was a significant difference before and after treatment with atomoxetine, as well as between the atomoxetine and placebo groups ( $P = 0.001$ ). In table 3, each

subclass of MACFIMS is described separately.

### Discussion

Impaired cognitive processing speed and episodic memory impairment are the most common CIs in MS, which are associated with additional problems in executive function, verbal psychology, and visual spatial analysis. In MS, cognitive decline often occurs at the early stages of the disease.<sup>13-15</sup> CVLT examines patients in language and memory area, SDMT examines processing speed/working memory area, and BVMT examines delayed recall and recognition.<sup>33</sup>

Various studies have been performed in patients with Parkinson's disease, depression, and primary and secondary psychotic disorders to assess the extent to which atomoxetine improves CI.

In the present study, most of the patients were of RR type.

**Table 3.** Brief Visuospatial Memory Test (BVMT) total, California Verbal Learning Test (CVLT) and Symbol Digit Modalities Test (SDMT) pretest and posttest

Group	BVMT pretest	n (%)	BVMT posttest	n (%)
Atomoxetine	Normal	15 (57.7)	Normal	18 (69.2)
	Abnormal	11 (42.3)	Abnormal	8 (30.8)
Placebo	Normal	18 (69.2)	Normal	18 (69.2)
	Abnormal	8 (30.8)	Abnormal	8 (30.8)
<b>CVLT pretest</b>				
Atomoxetine	Normal	12 (46.2)	Normal	20 (76.9)
	Abnormal	14 (53.8)	Abnormal	6 (23.1)
Placebo	Normal	16 (61.5)	Normal	17 (65.4)
	Abnormal	10 (38.5)	Abnormal	9 (34.6)
<b>SDMT pretest</b>				
Atomoxetine	Normal	12 (46.2)	Normal	20 (76.9)
	Abnormal	14 (53.8)	Abnormal	6 (23.1)
Placebo	Normal	16 (61.5)	Normal	17 (65.4)
	Abnormal	10 (38.5)	Abnormal	9 (34.6)

BVMT: Brief Visuospatial Memory Test; CVLT: California Verbal Learning Test; SDMT: Symbol Digit Modalities Test

In the case group, a significant improvement in cognitive domains was observed before and after atomoxetine administration, but in the placebo group, no significant improvement in cognitive domains was observed. This study showed that the changes in cognitive domains were significantly improved following the use of atomoxetine in the drug group compared to the placebo. Various studies have been performed to investigate the effects of atomoxetine on the improvement of cognitive disorders. A study showed that atomoxetine at a dose of 25-100 mg/day for 8 weeks improved executive function.<sup>27</sup>

Kehagia et al. also showed that atomoxetine improved problem solving, risk taking, and impulsive movement control.<sup>34</sup> Few studies have examined the effect of atomoxetine on cognitive improvement in patients diagnosed with depression. Weintraub et al. reported that atomoxetine was administered at 40 mg daily for 2 weeks and then increased to 40 mg twice a day for 10 weeks; although it had no effect on the treatment of depression, it improved cognition and daily sleep.<sup>28</sup> In another study, Borchert et al. showed that atomoxetine improved communication between the right inferior frontal gyrus (IFG) and dorsal anterior cingulate areas of the brain, resulting in improved speech psychology and mini-mental state examination (MMSE) test.<sup>31</sup> Warner et al. stated that atomoxetine use had a positive effect on several performance markers, including impulsivity, risk taking, and global cognition,<sup>30</sup> and a study in 2019 on patients with primary psychosis, especially schizophrenia, showed that this drug had no beneficial effect on the negative symptoms, but improved cognitive function.<sup>35</sup> The results of the present study are consistent with the above studies and show that the use of atomoxetine in appropriate doses and duration can improve the level of various cognitive domains in neurological and psychiatric disorders. Totally, MS is a debilitating physical and mental illness and is a major public health problem. This study showed that atomoxetine improved the cognitive domains after administration compared to placebo.

Atomoxetine is a modulator of dopamine uptake, which increases the extracellular level of dopamine in the prefrontal cortex (PFC). These effects of atomoxetine have made it less likely to be abused and less likely to cause tics and stereotypic movements compared to other stimulant drugs. Atomoxetine also increases the connection between the dorsal anterior cingulate and the

posterior lateral PFC, which are related to executive and cognitive functions.<sup>26-30</sup>

Atomoxetine has also been shown to increase extracellular levels of acetylcholine in the cerebral cortex and hippocampus, an effect that appears to be dependent on  $\alpha$ -1 norepinephrine or dopamine D1 receptor activation.

**Limitations:** According to the exclusion criteria, most of the participants in this study were women. This was a pioneering study in our country that has never been done before. Suggestions for future study include a larger-scale study of other neurological diseases and psychiatric disorders (primary psychosis or mood disorders) which cause CI.

## Conclusion

Cognitive impairment in MS is important and is associated with meaningful functional impairment and adverse effects on quality of life. The fact that cognitive impairment and associated disability can predate the onset of physical disability amplifies the importance of managing this aspect of the disease and maximizing clinical outcomes. Management of cognitive impairment may encompass slowing of further deterioration of impairment or improvement in already impaired cognition. Until this study, no effective drug for improving cognition in patients with MS had been introduced, and due to the importance of cognition, we investigated this issue. The aim of this study was to investigate the effect of atomoxetine on the cognitive function of patients with MS. The results of this study showed significant changes in the cognitive levels after taking atomoxetine compared to before medication, and also the atomoxetine group compared to placebo.

## Conflict of Interests

The authors declare no conflict of interest in this study.

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Informed consent was taken from the patients. If a person refused to participate in the study, she would not be deprived of any medical services. All personal data remained confidential (ethics ID: IR.AJUMS.HGOLESTAN.REC.1399.148).

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