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The effect of atomoxetine efficacy on freezing of gait in patient with Parkinson's disease: a double-blinded randomized clinical trial

Esmat Ramezanirad[1], Seyed Ehsan Mohammadianinejad[2], Davood Kashipazha[1], Gholamreza Shamsaei[1*], Mohammad Bahadoram[1,2]

[1]Department of Neurology, Golestan Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[2]Iranian Center of Neurological Research, Neuroscience Institute, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran

***Correspondence to**
Gholamreza Shamsaei, Email: shamsaei-gh@ajums.ac.ir and etermitant@protonmail.ch

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Abstract

Introduction: Freezing of gait (FOG) is a debilitating symptom experienced by many individuals with Parkinson's disease, characterized by an abrupt and transient inability to initiate or continue locomotion. Despite extensive research, effective pharmacological interventions targeting FOG remain elusive. Atomoxetine, a selective norepinephrine reuptake inhibitor, has shown promise in alleviating FOG in small-scale studies. However, the efficacy of atomoxetine in larger cohorts remains underexplored.

Objectives: This study aims to assess the impact of atomoxetine on Parkinson's disease-related FOG in a larger study population than currently reported in the literature.

Patients and Methods: This randomized clinical trial was performed in Golestan Hospital, Ahvaz, Iran, in 2022. The participants were divided into group A comprising 16 patients subjected to atomoxetine treatment, and group B consisting of 16 patients administered a placebo. Three scheduled visits were conducted. Freezing of Gait Questionnaire (FOGQ) scores was documented during each visit.

Results: The mean age of all participants was 62.4 ± 8.3 years, with no significant intergroup age disparity and no statistically significant gender-based distinctions between the two groups. The average disease duration in the atomoxetine group was 8.2 ± 3.1 years, while in the placebo group, it was 7.2 ± 3.4 years, with no significant divergence between the two groups. The study findings indicated no significant distinction in FOGQ scores between the treatment and placebo groups.

Conclusion: Though atomoxetine did not significantly improve improvement in freezing of the gait of studied patients with Parkinson's disease, it may cause a modest improvement in the gait freezing of some patients.

Trial Registration: The trial protocol was approved by the Iranian Registry of Clinical Trials (identifier: IRCT20211008052695N1; https://irct.behdasht.gov.ir/trial/59643, ethical code; #IR.AJUMS.HGOLESTAN.REC.1400.026).

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Introduction

Primary parkinsonism, also referred to as Parkinson's disease (PD), stands as the predominant cause of parkinsonism and ranks as the second most prevalent neurodegenerative disorder following Alzheimer's (1,2). This multifaceted disorder manifests through a complex interplay of genetic and environmental factors, leading to both sporadic and familial occurrences. Advanced age constitutes the principal risk factor, with a prevalence of approximately 0.5%-1% among individuals aged 65-69 years, escalating to 1-3% among those aged 80 years and above (2). Parkinsonism manifests through six primary symptoms, encompassing at-rest tremor, rigidity, bradykinesia-hypokinesia, stooped posture, loss of postural reflexes, and the phenomenon of freezing. Diagnosis necessitates the presence of at least two of these symptoms, one of which must be either resting tremor or bradykinesia (2,3). Prodromal symptoms of Parkinson's, including hyposmia, constipation, and sleep disorders, may manifest a decade or more before the onset of motor symptoms (4). Studies indicate the emergence of depression, fatigue, and urinary system disturbances approximately five years preceding the onset of PD (5). Asymmetrical symptom presentation at disease onset, coupled with a favorable response to levodopa, serves to reinforce the diagnosis of PD, presenting critical features in distinguishing it from other

Key point

Although some patients may experience modest improvements, atomoxetine treatment does not significantly improve the freezing of gait compared to the placebo group. This suggests that atomoxetine may not be an effective treatment option for this particular patient population. Further research is needed to identify alternative therapies that may yield better outcomes. However, some patients may experience modest improvements during atomoxetine treatment.

forms of Parkinsonism (6).

Freezing of gait (FOG) represents a prevalent and incapacitating symptom in Parkinson's patients, with a reported prevalence of approximately 27% (7,8). FOG is mostly observed in advanced PD and because of cooccurrence with postural imbalance can lead to falling. For this reason, the treatment of FOG is of notable importance. Current symptomatic treatments such as methylphenidate may be linked with hypertension and other vascular complications. Therefore, finding alternative symptomatic treatment options is an unmet need. Notably, FOG often exhibits resistance to dopamine agonist treatment in comparison to other Parkinson's symptoms, such as tremors, bradykinesia, and rigidity (8). Three distinct types of FOG exist; Dopamine-sensitive (the most common type), dopamine-induced, and dopamine-resistant (9). Instances of freezing commonly manifest during three scenarios: initiation of walking, attempts to turn around, and navigating through confined spaces, such as an elevator door. Simultaneous freezing and loss of postural reflexes pose a significant risk, leading to falls, disability, and mortality (1). While the anatomical and biochemical mechanisms underlying the FOG remain incompletely elucidated, certain studies suggest dysfunction in the basal nuclei and pedunculopontine nuclei in some cases. The best response to treatment in FOG of PD occurs in situations of dopaminergic deficiency such as in patients with a wearing-off state who benefit from increasing levodopa dose or frequency. However, this strategy might cause dyskinesia, especially in patients with advanced PD who are more likely to have trouble with FOG. Hence, the symptomatic treatment of FOG is an unmet need in many patients with advanced PD (10,11).

Prior research exploring various drugs for FOG treatment has identified levodopa as the most frequently employed medication. However, the efficacy of levodopa often necessitates high doses, potentially leading to dyskinesia. Consequently, ongoing investigations aim to identify a more suitable drug (12). Atomoxetine, a non-stimulant and selective norepinephrine reuptake inhibitor, has FDA approval for attention-deficit/hyperactivity disorder across various age groups (13-15). Numerous studies have explored the impact of atomoxetine on the cognitive deficits of Parkinson's patients, consistently revealing positive effects (16-19). Atomoxetine enhances prefrontal cortex function and frontostriatal connections, providing benefits for Parkinson's patients with pronounced frontostriatal structural abnormalities (20). Given the favorable outcomes of atomoxetine in ameliorating PD in some studies, the current investigation seeks to assess the drug's impact on improving the FOG in individuals with PD.

Objectives

This study aims to assess the impact of atomoxetine on PD-related FOG in a larger study population than currently reported in the literature.

Patients and Methods

Inclusion and exclusion criteria

Inclusion criteria encompassed individuals diagnosed with PD according to the criteria outlined by the Movement Disorder Society. Participants were required to be with a Hoehn and Yahr stage of 2 or 4 of any sex and age. Exclusion criteria included individuals with a history of significant cardiac arrhythmias, uncontrolled hypertension, or psychiatric disorders requiring immediate intervention.

Sampling

The study recruited a total of 32 participants meeting the inclusion criteria. To determine the sample size, by reviewing the literature and previous studies and taking into account the special purpose of freezing changes in walking in Parkinson's patients as the main outcome of the study, a 5% error level was used to determine the sample size. To determine the sample size, Cochran's formula was used. In the formula, alpha 0.5 and beta 0.2 were taken into account, and the sample size in each group was equal to 16 people with PD referred to Ahvaz Golestan hospital in 6 months in 2021. All the patients who met the inclusion criteria and did not meet the exclusion criteria were selected as the sample and this work continued until the final sample size was reached.

Randomized or allocation

Participants were randomly assigned to either group A or group B using the random block method with blocks of 4. Blocking is used to balance the number of samples allocated to each of the studied groups. This feature helps in cases where intermediate analyses are needed during the sampling process, the number of samples allocated to each group stays equal.

Blinding

To prevent disclosure of the allocation in each block, we used the blinding method. The trial was conducted under double-blind conditions, meaning both participants and researchers remained unaware of the treatment assignment throughout the study. Blinding was maintained through the use of identical-appearing medication packs labeled only with participant identification numbers.

Intervention

Group A included 16 patients who an uninformed person randomly selected. This group was treated with 40 mg atomoxetine for 2 weeks. Then their drug dose was increased to 80 mg for six weeks. Group B included 16 patients who an uninformed person randomly selected. This group was treated with a placebo with the same dose as group A. The first visit was on the first day and before the start of treatment. In this visit, the score was determined using the FOGQ questionnaire. The second visit was done two weeks after the start of the treatment and the third visit was done 6 weeks after the second visit, and in each visit, the patient's FOGQ questionnaire score was recorded.

Data tool validity

The FOGQ, employed as an investigative tool for FOG in parkinsonian patients, has been validated. It comprises six questions graded on a scale of 0 to 4, yielding a total score range from 0 to 24. The validity and reliability of the questionnaire were established on a cohort of 40 PD patients, obtaining a Cronbach's alpha of 94% and a validity rate of 70% (22). Additionally, the Iranian version of the FOGQ, translated by Taghizadeh in 2021, demonstrated robust psychometric properties when administered to 115 PD patients, yielding a Cronbach's alpha of 92% (23).

Data collection

FOGQ scores were recorded at the initial visit, conducted on the day before treatment initiation, as well as at subsequent visits occurring at two weeks and six weeks post-treatment initiation.

Statistical analysis

To analyze the data, descriptive statistics methods were first used to describe the studied variables, including frequency distribution tables, and central and dispersion indices. In quantitative variables, frequency, mean, or median were used to describe data, and standard deviation or interquartile range was used to describe data dispersion. The normality of quantitative data was checked using the Kolmogorov-Smirnov test. Intra-group comparisons were performed with paired *t* test and between-group comparisons were performed with independent *t* test . The chi-square test was used for qualitative variables analysis. The significance level of the tests was considered less than 0.5. Data analysis was done using SPSS 22 software.

Results

This study involved a total of 32 patients divided into two distinct groups, with 16 individuals in the atomoxetine group and 16 in the placebo group (Figure 1).

The mean age for all participants was 62.4±8.3 years.

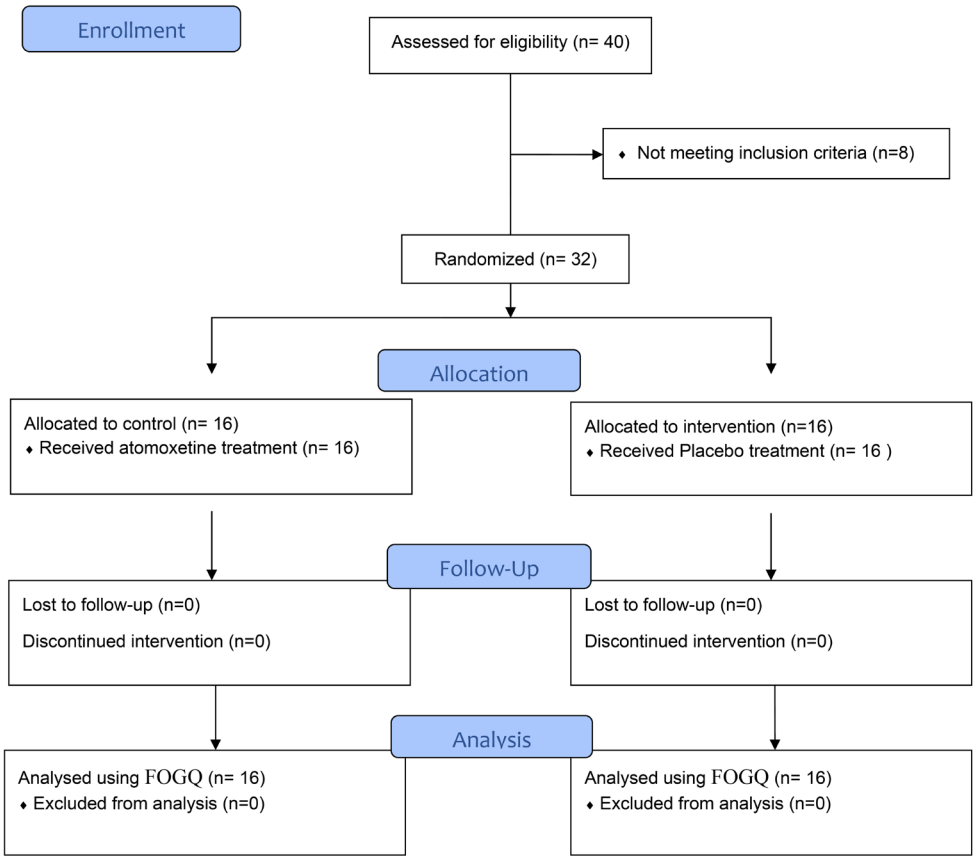

Figure 1. CONSORT flow diagram of the study population.

Specifically, the mean age within the atomoxetine group was 64.2±7.9 years, while in the placebo group, it was 60.5±8.6 years. Statistical analysis revealed no significant difference in age between the atomoxetine and placebo groups. The age and gender distribution between the atomoxetine and placebo groups did not exhibit any significant differences. Additionally, analysis of disease duration demonstrated no statistically significant disparity between the average duration of the disease of the two groups.

Utilizing the Kolmogorov-Smirnov test, it was determined that the data distribution within both the atomoxetine and placebo groups adhered to a normal distribution. Subsequently, an independent t-test was employed to compare the respective quantities between the two groups. Table 1 comprehensively examines the total FOGQ scores between the atomoxetine and placebo groups, delineated by treatment duration. Notably, the two groups had no statistically significant difference in the total FOGQ scores. The detailed comparison of patients within the atomoxetine and placebo groups is presented in Tables 2 and 3.

Discussion

The current investigation demonstrated that the administration of atomoxetine during a treatment regimen involving doses of 40 mg for two weeks and 80 mg for six weeks exhibited an improvement in the FOGQ scale in comparison to the placebo group. However, it is noteworthy that this effect did not attain statistical significance. Numerous analogous studies have explored the impacts of diverse medications on distinct FOG performance in PD patients.

Considering the involvement of the noradrenergic system in PD patients with compromised executive function and FOG, especially in instances of dopamine agonist resistance, the examination of atomoxetine as a noradrenergic system enhancer was deemed pertinent. A pilot study by Marsh et al in 2009, involving 12 PD patients with executive function impairment, revealed that atomoxetine, at a dosage of 25 mg per day for eight weeks (up to a maximum of 100 mg), led to improved executive function (16). Kehagia et al in 2014 investigated the impact of a 40 mg dose of atomoxetine on 25 Parkinson's patients, demonstrating enhancement in problem-solving, risk-taking, and impulsive movement control (24). A 2016 study comparing atomoxetine to a placebo found that atomoxetine enhanced functional connectivity between brain regions. This improvement led to better speech fluency and higher scores on the Mini-Mental State Examination (MMSE) (25). Warner et al, in a study on the effect of atomoxetine on executive function disorders in PD patients, reported improvements in executive functions (19). Few studies have specifically explored the effects of atomoxetine on FOG, with these inquiries often confined to pilot studies. Jankovic et al conducted a double-blind study in 2009, involving 10 PD patients experiencing FOG (5 treated with atomoxetine and 5 with placebo), revealing non-significant differences. Similarly, Revuelta et al investigated the impact of atomoxetine on levodopa-resistant FOG in 10 PD patients, finding non-significant differences after 8 weeks of treatment (26,27). These findings align with the outcomes of the present study, where improvement in the FOGQ scale compared to the placebo group was observed, yet this improvement

Table 1. Demographic and statistical characteristics of the study population divided into atomoxetine and placebo groups

Demographic features		Atomoxetine group (n=16)	Placebo group (n=16)	Total (N=32)	*P* value
Age (years), Mean ± SD		64.2 ± 7.9	60.5 ± 8.6	62.4 ± 8.3	0.120*
Gender distribution	Male (%)	9 (53.1%)	9 (53.1%)	17 (53.1%)	0.080**
	Female (%)	7 (49.6%)	7 (49.6%)	15 (53.1%)	

SD: Standard deviation.
*Independent *t* test; ** Chi-square.

Table 2. Comparison of atomoxetine and placebo group patients, according to the progress of treatment

Variables	Group	Mean (SD)	*P* value
FOGQ total score before starting atomoxetine and after 2 weeks	Before atomoxetine	10.8 (4)	0.170*
	After 2 weeks	8.8 (4.1)	
Total FOGQ score before starting atomoxetine and after 6 weeks	Before atomoxetine	10.6 (4)	0.110*
	After 6 weeks	8.5 (4.1)	
Total FOGQ score 2 weeks and 6 weeks after starting atomoxetine	After 2 weeks of atomoxetine	8.9 (4)	0.760*
	After 6 weeks of atomoxetine	8.5 (4.2)	
FOGQ total score before starting placebo and after 2 weeks	Before starting the placebo	10.1 (5)	0.950*
	After 2 weeks	9.8 (4.8)	
Total FOGQ score before starting placebo and after 6 weeks	Before starting the placebo	10.1 (5)	0.930
	After 6 weeks	9.8 (5)	
FOGQ total score 2 weeks and 6 weeks after starting placebo	After 2 weeks	9.8 (4.8)	0.950
	After 6 weeks	9.8 (4.9)	

SD: Standard deviation; FOGQ: Freezing of Gait Questionnaire.
*Paired *t* test.

Table 3. Comparison of atomoxetine and placebo group patients according to the progress of treatment

Variable	Group	Mean (SD)	*P* value
FOGQ total score before treatment	Atomoxetine	10.8 (4)	0.620*
	Placebo group	10 (5.1)	
Total FOGQ score after 2 weeks	Atomoxetine	7.8 (4.1)	0.420*
	Placebo group	9.8 (4.8)	
Total FOGQ score after 6 weeks	Atomoxetine	8.3 (4.4)	0.350*
	Placebo group	9.9 (5)	

SD: Standard deviation; FOGQ: Freezing of Gait Questionnaire.
*Independent *t* test.

did not reach statistical significance. Importantly, no adverse effects were noted in the current study.

Other investigations have explored drug treatments for FOG. Studies on the effectiveness of levodopa in reducing FOG in PD patients, involving 19 and 20 participants, demonstrated a significant reduction in FOG (28,29). Despite dopamine's involvement in FOG mechanisms, the effectiveness of dopamine agonists in treating this condition has not been proven consistently satisfactory in conducted studies (30-32). In conclusion, this study sheds light on the potential impact of atomoxetine on the FOG in PD patients. The findings indicate a trend towards improvement in the FOGQ scale with atomoxetine treatment, although statistical significance was not achieved in comparison to the placebo group. These results align with previous pilot studies on atomoxetine's effects on FOG. Notably, the investigation contributes to the growing body of literature exploring the role of noradrenergic modulation in PD symptomatology, specifically addressing FOG. However, it is essential to acknowledge certain limitations in this study, including the relatively small sample size, the short treatment duration, and the absence of a long-term follow-up. Additionally, the diverse nature of FOG manifestations and the multifactorial etiology of PD pose challenges in discerning specific therapeutic effects. Future research endeavors with larger cohorts, extended treatment durations, and comprehensive assessments are warranted to further elucidate the potential benefits of atomoxetine in managing FOG in PD patients.

Conclusion

In conclusion, the study found that atomoxetine treatment did not result in statistically significant improvements in the outcomes of interest compared to placebo in the study population. While some patients reported modest improvements during atomoxetine treatment, these subjective experiences did not translate into significant differences at the group level. These findings suggest that atomoxetine may not be an effective treatment option for this particular patient population, and further research is needed to identify alternative therapies that may yield better outcomes.

Limitations of the study

Some limitations of this study should be acknowledged. Firstly, the relatively small sample size of 32 participants may have limited the statistical power to detect subtle differences between the treatment and placebo groups. Additionally, the short duration of the trial and the limited number of scheduled visits may not have provided sufficient time to observe the full effects of atomoxetine on FOG. Furthermore, the study did not consider potential confounding variables such as concomitant medications or disease severity, which could have influenced the outcomes.

Authors' contribution

Conceptualization: Esmat Ramezanirad, Gholamreza Shamsaei.
Data curation: Mohamad Bahadoram.
Formal analysis: Gholamreza Shamsaei, Mohamad Bahadoram.
Funding acquisition: Esmat Ramezanirad.
Investigation: Esmat Ramezanirad, Gholamreza Shamsaei, Seyed Ehsan Mohammadianinejad.
Methodology: Esmat Ramezanirad, Seyed Ehsan Mohammadianinejad.
Project administration: Esmat Ramezanirad, Gholamreza Shamsaei.
Resources: Mohamad Bahadoram.
Software: Seyed Ehsan Mohammadianinejad.
Supervision: Gholamreza Shamsaei, Mohamad Bahadoram.
Validation: Esmat Ramezanirad, Seyed Ehsan Mohammadianinejad.
Writing–original draft: Esmat Ramezanirad, Davood Kashipazha.
Writing–review & editing: Mohamad Bahadoram, Davood Kashipazha.

Conflicts of interest

The authors declare that they have no competing interests.

Data availability statement

The data that support the findings of this study, excluding the identity information of the patients, are available on request from the corresponding author.

Ethical issues

The research was conducted in accordance with the principles of the Declaration of Helsinki and received approval from the Institutional Review Board (IRB) of Ahvaz Jundishapur University of Medical Sciences (#IR.AJUMS.HGOLESTAN.REC.1400.026). Accordingly, written informed consent was taken from all participants before any intervention. This study was derived from the thesis project of Dr. Esmat Ramezanirad in neurology (Thesis #330098319). Moreover, The trial protocol was approved by the Iranian Registry of Clinical Trials (identifier: IRCT20211008052695N1; https://irct.behdasht.gov.ir/trial/59643).

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