Abstract

Objectives
Stuttering is a common problem at all ages that is required to be treated since childhood. Atomoxetine is currently used for the treatment of attention deficit hyperactivity disorder (ADHD). It can be effective for the treatment of stuttering due to its selective inhibition of norepinephrine reuptake and dopaminergic properties. Therefore, this randomized controlled trial aimed to evaluate the effect of atomoxetine on children’s stuttering.

Materials & Methods
The children aged 4-12 years and diagnosed with stuttering, referred to Pediatric Neurology and Psychology clinics, were randomly divided into experimental (n=50) and control (n=50) groups. One group received atomoxetine plus speech therapy, and the other group received only speech therapy. Both groups completed the Stuttering Severity Instrument-Fourth Edition at the baseline (on the first visit) and 3 months after the intervention. The results were compared between the two groups using SPSS software (version 21).

Results
Most of the children (67%) were male. Moreover, 24%, 46%, and 30% of the subjects were within the age ranges of < 60, 60-95, and > 95 months, respectively. Nearly half of the patients (52%) had a positive family history of stuttering. Stuttering severity was the highest within the age range of 60-95 months, in left-handed children, in those who used formula, and in those who felt insecure in the family; however, there was no difference in stuttering severity based on child’s gender, concomitant ADHD, multilingualism, facial or movement tics,
Introduction

Stuttering is a communication disorder that impairs the rhythm, continuity, and fluency of the individual’s speech with frequent repetitions or prolongations of sounds/syllables without problems in voice or articulation/phonology (1). The overall incidence of stuttering is reported at about 5%, generally starting in the early stages of life (2). Stuttering is more common in male children. Nearly half of the cases have a positive family history (3). Those with a positive family history began stuttering earlier and tend to have more linguistic and attentional vulnerabilities (4). Most cases naturally recover until teenage, except in rare cases secondary to emotional trauma or brain damage, which persist until adulthood (5). As it cannot be anticipated whether stuttering recovers spontaneously or not, treatment is suggested to be started early for all patients (6). Behavioral therapies, especially speech therapy, are the main treatment of stuttering (6); however, the aforementioned treatments cannot influence the brain changes of stuttering, including hyperactivity, abnormal coordination of brain regions, and dopamine (DA) dysregulation (7). Therefore, medical treatment might be more effective.

Atomoxetine is a nonstimulant selective norepinephrine (NE) reuptake inhibitor with region-specific shared monoamine uptake inhibition and low affinity for 5-hydroxytryptamine (serotonin) and DA uptake sites, efficiently absorbed after oral administration (8). Atomoxetine was introduced in the United States and approved by the United States Food and Drug Administration in 2002. Atomoxetine is currently used for the acute and maintenance treatment of pediatric attention deficit hyperactivity disorder (ADHD) (9, 10). The evidence suggests that several cases of stuttering, especially severe cases, are associated with ADHD (11, 12), and the patients with ADHD have stuttering-like disfluency (13).

Accordingly, the current study hypothesized that atomoxetine could also be effective in the treatment of stuttering by a rapid increase of NE in the occipital cortex, lateral hypothalamus, dorsal hippocampus, and cerebellum and extracellular levels of DA. Therefore, this double-blind, randomized controlled trial (RCT) aimed to evaluate the effect of atomoxetine on the severity of children’s stuttering and evaluate the association of different patients’ characteristics with stuttering severity.
Materials & Methods
The study population included all children aged 4-12 years referred to a pediatric speech therapy clinic diagnosed with stuttering. The sample size was considered 47 subjects, based on 53% efficacy of speech therapy in stuttering (14) and supposing 30% efficacy of atomoxetine in stuttering. Considering the risk of loss to follow-up, 50 participants were included in each group. The researcher selected the participants based on the inclusion criteria using the census method until 100 children were included. The children with neurodegenerative disorders, neurodevelopmental disorders, and the use of drugs affecting the central nervous system were not included in the study.

The researcher explained the study objectives to the children’s parents and asked them to read and sign the written informed consent if they agreed that their child would participate in the study. The included children were randomly divided into experimental (n=50) and control (n=50) groups using a systematic randomization method. The randomization sequence was generated by the researcher, and the patient and the analyzer were unaware of the group allocations. The experimental group received 0.5 mg/kg atomoxetine (Atiyeh Novin Co., Iran) and was scheduled for speech therapy for 3 months. The speech therapy was performed by an expert speech therapist during individual sessions with the patients, held three times a week, each for 45 minutes. The control group only received speech therapy with the same protocol.

Both groups completed the Stuttering Severity Instrument-Fourth Edition (SSI-4) at the baseline (on the first visit) and 3 months after the intervention. This questionnaire evaluates the participant’s stuttering severity by 10 self-report items, including 1 items for perceived stuttering severity, 3 items for the locus of control, and 4 items for amounts of avoidances and 2 items for Avoidance and locus of control. The total score is calculated by the sum of answers to the items. The Persian version of this questionnaire was used in the present study, which was previously validated by Tahmasebi et al. (15).

The researcher collected the child’s information during history taking and physical examination and recorded the child’s age and gender, family history of stuttering, hand dominance, using formula and teats, concomitant ADHD, multilingualism, facial or movement tics, sleeping hours, and feeling insecure in the family in the study’s checklist. The children who showed any adverse effects of the drugs and those who did not refer for the 3-month follow-up were excluded from the study.

Statistical Analysis
The results were presented as frequency (percentage) for categorical variables and mean±standard deviation for quantitative variables. The one-sample Kolmogorov-Smirnov test was used to assess the normal distribution of the data, and the equality of variances between the groups was confirmed by Levene’s test (P=0.503). The continuous variables were compared using the independent samples t-test or Mann-Whitney U test whenever the data did not appear to have normal distribution or when the assumption of equal variances was violated across the study groups. On the other hand, the categorical variables were compared using the Chi-square test. The statistical software IBM SPSS Statistics for Windows (version 21.0; IBM Corp. 2012. Armonk, NY: IBM Corp.) was used for statistical analysis. P-values less than 0.05 were considered statistically significant.
Results
A total of 100 children completed the study. Most of the children (67%) were male. Moreover, 24%, 46%, and 30% of the subjects were within the age ranges of < 60, 60-95, and > 95 months, respectively. Nearly half of the subjects (52%) had a positive family history of stuttering. Furthermore, 50 children were evaluated in each group (Figure 1). Table 1 shows the demographic characteristics of the participants of the two study groups. As indicated, the groups did not have a significant difference in demographic characteristics (P>0.05; Table 1).

The mean values of stuttering severity in the experimental group were 2.84±1.01 and 2.08±0.96 at the baseline and 3 months after the intervention, respectively. The mean values of stuttering severity in the control group were 2.48±0.86 and 2.10±0.95 at the baseline and 3 months after the intervention, respectively. The comparison of the mean stuttering severity after 3 months to baseline values showed a significant decrease in the experimental group (P<0.001) and the control group (P<0.001). The mean stuttering severity was not different between the control and intervention groups at the baseline (P>0.05) but significantly different after 3 months (P=0.011).

Stuttering severity was the highest within the age range of 60-95 months in the intervention group (P<0.001; Table 2) but not different based on other variables in this group (P>0.05; Table 2). Stuttering severity was higher in the left-handed children (P=0.027), those who used formula (P=0.007), and those who felt insecure in the family (P=0.009). However, there was no difference in stuttering severity based on the child’s gender, concomitant ADHD, multilingualism, facial or movement tics, sleeping hours, and using teats (P>0.05; Table 3).

Table 1. Demographic Characteristics of Studied Patients in Experimental and Control Groups

| Age (month) | Total | Intervention group | Control group | P-value † |
|-------------|-------|-------------------|---------------|-----------|
| <60         | 24    | 5                 | 19            | 0.003     |
| 60-95       | 46    | 25                | 21            |           |
| >95         | 30    | 20                | 10            |           |
| Mean±SD     | 74.88±26.30 | 72.36±30.82 | 77.40±20.70   | 0.341     |
| Gender      |       |                   |               |           |
| Female      | 33    | 14                | 19            | 0.288     |
| Male        | 67    | 36                | 31            |           |
| Schooling   |       |                   |               |           |
| Student     | 35    | 20                | 15            | 0.295     |
| Below school age | 65 | 30                | 35            |           |
| Positive family history | 52 | 28 | 24 | 0.423 |
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| Stuttering initiation | <3 years | 3 years | 3.5 years | >3.5 years | *Mean±SD* |
|-----------------------|---------|---------|-----------|------------|-----------|
|                       | 14      | 29      | 27        | 30         | 41.4±11.94|
|                       | 2       | 15      | 13        | 20         | 40.68±15.91|
|                       | 12      | 14      | 14        | 10         | 42.12±5.63|

*The results of the Chi-square test were considered significant in case of *P*<0.05.*

SD, standard deviation
Discussion
In the present study, a total of 100 children with stuttering were evaluated, most of whom were male subjects. Nearly half of the children were within 60-95 months, and 65% were below the school age. The aforementioned demographics are in line with the results of epidemiological studies, reporting a higher incidence of stuttering in male cases (2). Although treatment is suggested to be initiated as early as possible, the treatment of children who stutter is more difficult, especially those below school age (16).

As a multifactorial condition, several risk factors have been identified for stuttering. One of the important associated factors is anxiety, observed in most patients with stuttering, which might reflect the social reaction to their speech problems (17), such as bullying, social isolation, low self-esteem, satisfaction with life (18), and impaired quality of life (19). In the present study, the patients’ anxiety level was not evaluated; however, there was a higher stuttering severity in children who felt insecure in the family. Family problems are the source of stuttering itself; furthermore, the treatment of stuttering requires the coordination of the family members to improve the child’s problem (20, 21). Therefore, also shown in the current study, family and feeling insecure in the family are important factors for stuttering severity (22).

Another important aspect observed in the present study is the use of formula, which has been associated with a higher stuttering severity, compared to the breastfed children. This finding can be attributed to the effect of a mother’s support and feeling secure on the reduction of stuttering severity and the protective effect of two fatty acids, including omega 3 and 6, detected in human milk against stuttering (23). This finding implies the possible mechanism of diet on neurodevelopment and stuttering (24). It is required to carry out further studies in this regard.

It has been observed that more than half of the children with stuttering have a positive family history associated with articulation problems (25). In the present study, 52% of the children had a positive family history of stuttering; however, stuttering severity was not different based on a positive family history according to the results of the present study, which could be due to the multifactorial nature of stuttering and the effect of other variables on stuttering severity. Several functional, anatomical, neurological, and neurodevelopmental abnormalities have been reported in children with stuttering (26, 27). Along with the neurological disorders in stuttering, left-handedness has also been shown to be associated with stuttering, as both are associated with weak laterality (28). The results of the current study also showed that left-handedness is associated with higher stuttering severity. As the exact pathophysiology of stuttering is still unknown, further studies are required to determine the etiology of the brain and neuronal alterations during stuttering.

The comparison of the two groups with similar demographics in the present study showed that both groups receiving speech therapy with or without atomoxetine had a significant reduction in stuttering severity after the 3-month treatment period. These results confirmed the efficacy of speech therapy on children’s stuttering, suggested as the mainstay of treatment, especially when performed by a qualified speech-language pathologist (6, 7). During speech therapy, also known as “fluency shaping” or “prolonged
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In the present study, speech therapy was given to all the participants by a speech therapist. Scoring the participants’ stuttering based on the SSI-4 showed a statistically significant reduction in the scores after the 3-month treatment period. On the contrary, some speech and language therapists treating a total of 2036 children who stutter reported the minor effect of speech therapy and other techniques with a total recovery rate of about 14% (30). These controversies can be due to the multifactorial nature of stuttering and the natural recovery of numerous cases. Furthermore, the follow-up period is different among studies, and some studies have considered the long-term efficacy of treatments (31, 32).

In addition to behavioral therapy, few alternatives or complementary treatment methods have been suggested for the management of stuttering (33). The present study showed that the addition of 3 months of oral atomoxetine administration to the routine speech therapy resulted in a greater decrease in children’s stuttering severity, compared to the group receiving speech therapy alone. Atomoxetine is a nonstimulant drug with a significant effect on ADHA (9, 10). It is supposed that the mechanism of action for the efficacy of this nonstimulant drug includes reduced speech pressure and higher social abilities. Although atomoxetine has not been previously used for the treatment of stuttering, a study performed by Donaher et al. reported a higher rate of stuttering, tics, and social anxiety using the stimulant drug Adderall XR®, compared to those by Strattera® (34). Although the findings of this study confirm the presented hypothesis, it was limited in terms of the study type (case study) and was not focused on stuttering. Therefore, further studies are required to determine the exact mechanism of action of atomoxetine on stuttering. It has been previously reported that several cases of stuttering, especially severe cases, are associated with ADHD (11, 12). The results of the present study also showed that 26% of children with stuttering had ADHD, which confirms the concomitance of stuttering and ADHD; nevertheless, stuttering severity was not different based on concomitant ADHD in children. Other factors, such as using teats, tics, duration of watching TV or sleeping, patients’ age, and age of stuttering initiation, were not associated with stuttering severity in the present study.

The present double-blind RCT clearly showed the efficacy of the addition of atomoxetine to routine speech therapy in the treatment of stuttering in children. However, this study had some limitations. Firstly, the effect of treatment was evaluated after the end of the treatment period (i.e., 3 months), and long-term follow-up was not considered. Therefore, the long-term efficacy of the treatments was not evaluated. Secondly, the participants were selected from referrals to one center and recruited into the study by the census method, which increases the chance of the census method, which increases the chance of the effect of confounders on the study results, such as the social class, economic status, and cultural and geographical factors. Thirdly, this study did not evaluate the pure effect of atomoxetine and could only assess the impact of its combination with speech therapy due to the ethical considerations of depriving the child of the
previously confirmed treatment strategy.

**In conclusion**
the results of the present study showed that atomoxetine is an effective complementary treatment to be used in addition to speech therapy in the treatment of children’s stuttering. Therefore, it is suggested to consider this treatment in the clinical guidelines for treatment strategies for stuttering in children. Further studies are required to evaluate the pure efficacy of this drug, its effectiveness in adults with stuttering, and the mechanism of action of this drug on stuttering.

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**Author’s Contribution**
Farzad Ahmadabadi: Designed and conceptualized the study and revised the manuscript.
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Ghazal Zahed and Farshid Shahriyari: Visited the patients and Drafted the issue

**Conflict of interest**
The present study was not financially supported by anyone

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