Atomoxetine as an adjunct to nonpharmacological treatments for preventing vasovagal attacks in patients with recurrent vasovagal syncope: A pilot randomized-controlled trial

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ABSTRACT

Background: Despite the reduced quality of life in patients with recurrent vasovagal syncope (VVS), pharmacologic treatment options remain limited. Studies indicate that norepinephrine reuptake inhibition reduces tilt-induced syncope/pre-syncope. This study aimed to evaluate the effects of atomoxetine on syncopal/pre-syncopal episodes in patients with recurrent VVS.

Methods: In a placebo-controlled trial, we randomized patients with newly diagnosed VVS who experienced ≥3 syncopal episodes in the past three months to receive either atomoxetine (20 mg daily for two weeks followed by 40 mg daily for two weeks) or placebo. The primary endpoint was the combined number of syncopal and pre-syncopal episodes.

Results: Among 843 patients initially screened, 46 were randomized (N = 23 in each group) and reevaluated at one and three months. Compared to placebo, atomoxetine significantly reduced the primary endpoint after three months ($P < 0.001$). In the atomoxetine arm, the median time to first pre-syncopal episode was 55 days (95% confidence interval (CI): 41.21–68.79), while this was 27 days (95% CI: 14.48–39.52) for the placebo group ($P < 0.001$). In a subgroup analysis of patients with systolic blood pressure < 110 mmHg, atomoxetine reduced the primary endpoint, and the number of syncopal and presyncopal episodes after one and three months. In this subgroup, the median time to first pre-syncopal attack was 56 days in the atomoxetine group as opposed to 9 days in the placebo group.

Conclusions: In this pilot study, the promising effects of atomoxetine in reducing syncopal/pre-syncopal episodes in recurrent VVS, especially with low blood pressure phenotype, warrant the conduction of future randomized trials.

1. Introduction

Syncope accounts for 0.8–2.4% of emergency visits, imposing a considerable financial burden on the health system [1,2]. Notably, in patients with recurrent syncope, the quality of life impairment is comparable with chronic conditions such as severe rheumatoid arthritis [3,4], chronic low back pain [3,4], and epilepsy [3–5]. The most common type of syncope is vasovagal syncope (VVS)

which is characterized by hypotension that can manifest with or without a drop in heart rate [1,2,6]. Despite its high burden, the American College of Cardiology/American Heart Association [1] and the European Society of Cardiology [2] found insufficient evidence to recommend any pharmacological treatment with higher than IIa and IIb class of recommendation, respectively, which is arisen mostly from the poorly understood pathophysiology of VVS. This is while patients with recurrent VVS who receive lifestyle modification recommendations still experience spells that interfere with their daily functions [1,2].

Vaddadi and colleagues [7] found that patients with VVS have lower norepinephrine spillover compared with control subjects, which may play a role in inducing syncope. Theoretically, inhibi-

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tion of norepinephrine reuptake transporter (NET) results in delayed reuptake of norepinephrine in synaptic clefts, which in turn causes increased norepinephrine spillover and may prevent the spell. This hypothesis has been evaluated in healthy individuals by sibutramine or reboxetine, which reduced head-up tilt test (HUTT)-induced syncope and pre-syncope by 78% [8]. Furthermore, in an open-label series of highly symptomatic patients with VVS, sibutramine reduced the frequency of vasovagal spells [9]. In a recent proof of principle study, atomoxetine reduced the number of HUTT-induced syncope by about 50% compared to placebo [10]. Additionally, a recent systematic review and meta-analysis demonstrated beneficial effects of NET inhibitors in preventing HUTT-induced VVS in patients with VVS and healthy individuals [11]. Therefore, it appears that a randomized clinical trial of atomoxetine in patients with VVS is warranted.

In this pilot double-blind placebo-controlled randomized clinical trial, we aimed to evaluate the effectiveness of atomoxetine, as a novel treatment, on preventing syncopal and pre-syncopal episodes in patients with recurrent VVS.

2. Methods

2.1. Ethical considerations and registration

The scheme of this clinical trial was approved by the Research Ethics Committee of School of Medicine, Tehran University of Medical Sciences (IR.TUMS.MEDICINE.REC.1397.273) and it complied with the Declaration of Helsinki. Participation required written informed consent. In case of age <18 years, parents of the patient were asked to provide informed consent. The protocol of this study has been registered in the Iranian Registry of Clinical Trials (IRCT20180125038507N1).

2.2. Trial design

We conducted a pilot randomized controlled trial to examine the efficacy of atomoxetine in patients with a high burden of VVS. Patients were recruited from referrals to the Syncope Unit of Tehran Heart Center [12] at Tehran University of Medical Sciences. Eligible participants were randomized to two parallel treatment groups with a 1:1 ratio to receive either atomoxetine or placebo. The randomization code was generated by computer for permuted blocks of four. Medications were identical in shape and color and were prepared in sequentially numbered opaque sealed envelopes. The recruiting physician was not aware of the random sequence generation process. The patients, the physicians who gave out the medication envelopes and the investigators who assessed baseline and follow-up variables were all blinded to the randomized intervention.

2.3. Trial population and eligibility criteria

Individuals with newly diagnosed VVS were evaluated for eligibility. VVS was diagnosed based on the clinical history, physical examination, and the description provided by eyewitnesses. According to syncope guidelines, the diagnosis was assumed if features compatible with VVS were identified. In cases with equivocal initial clinical work-ups, the presence of a response compatible with VVS was confirmed by HUTT [1,2]. Type of the response to the HUTT was defined according to the modified Vasovagal Syncope International Study classification [13]. We included patients with the definitive diagnosis, and the patients with equivocal history and diagnostic work-ups were excluded [1,2]. The baseline blood pressure was measured with an oscillometric device (OMRON M6 Comfort) during the office visit. All readings were taken from the left arm at the level of the heart, after five minutes of resting in a quiet examination room in a sitting position with back supported and feet on the ground. The blood pressure was measured twice, with an interval of 1–2 min between readings, and the first measurement was discarded [14].

Patients were eligible if they were 10–70 years of age and had three or more VVS episodes in the last three months. Key exclusion criteria included other potential causes of syncope, a 30 beats/min or higher increase in heart rate (postural orthostatic tachycardia syndrome) or a decrease of 20 mmHg in systolic blood pressure, or 10 mmHg in diastolic blood pressure, or more (orthostatic hypotension) after a standard standing test, ever receiving medications for VVS, use of monoamine oxidase inhibitors or selective serotonin reuptake inhibitors, documentation of rhythm disorders that may explain syncope, structural heart disease, heart failure, renal disease, history of an episode of loss of consciousness other than syncope, hypertension, closed-angle glaucoma, pregnancy, and inability or refusal to provide informed consent.

2.4. Interventions

All patients were provided with counseling about the generally benign nature of their episodes and potentially helpful measures (i.e., identification and avoidance of possible triggers, lying down during the prodromal phase, increasing the daily fluid and salt intake). Participants were instructed to use physical counter-pressure maneuvers like handgrip, arm tensing, leg crossing, and squatting in situations where they are susceptible to VVS, and to abort an imminent VVS episode if the prodromal symptoms were identifiable [15].

Both arms received their medications in packets for 28 days. The intervention arm received atomoxetine at a daily dose of 20 mg for the first two weeks, followed by atomoxetine 40 mg per day for 14 days if they experienced no issues tolerating the medication. Studying polymorphisms of the cytochrome P450 2D6 enzyme, the principal metabolizer of atomoxetine [16], revealed that 35–39% of the Iranian people are poor or intermediate metabolizers [17,18]. This profile predisposes Iranian patients to the adverse effects of atomoxetine. Hence, we administered a low dose of atomoxetine for just one month to minimize its probable side effects and the possibility of drop-out [16]. The placebo group received their medication with the same instructions. The follow-up visits were planned at one and three months after randomization. Such follow-up duration was deemed reasonable due to the high possibility of VVS recurrence in patients with ≥3 episodes over the past three months, and due to the novelty and the pilot setting of this trial.

2.5. Endpoints

The primary efficacy endpoint was the sum of syncopal and pre-syncopal episodes at one and three months. Syncope was defined as an abrupt, transient, and total loss of consciousness, associated with loss of postural muscle tone. Pre-syncope was defined as a near but incomplete loss of consciousness, associated with symptoms usually perceived before VVS. Patients were instructed to fill out pre-specified forms (Supplementary Material 1) in order to keep records of the occurrence and time of syncopal and pre-syncopal events. We extended the follow-up duration to three months to look for delayed drug effects [19] in patients as an exploratory analysis. The primary safety endpoint was defined as the occurrence of any adverse event at one and three months. Moreover, we evaluated time to the first syncopal and pre-syncopal episodes as secondary endpoints.
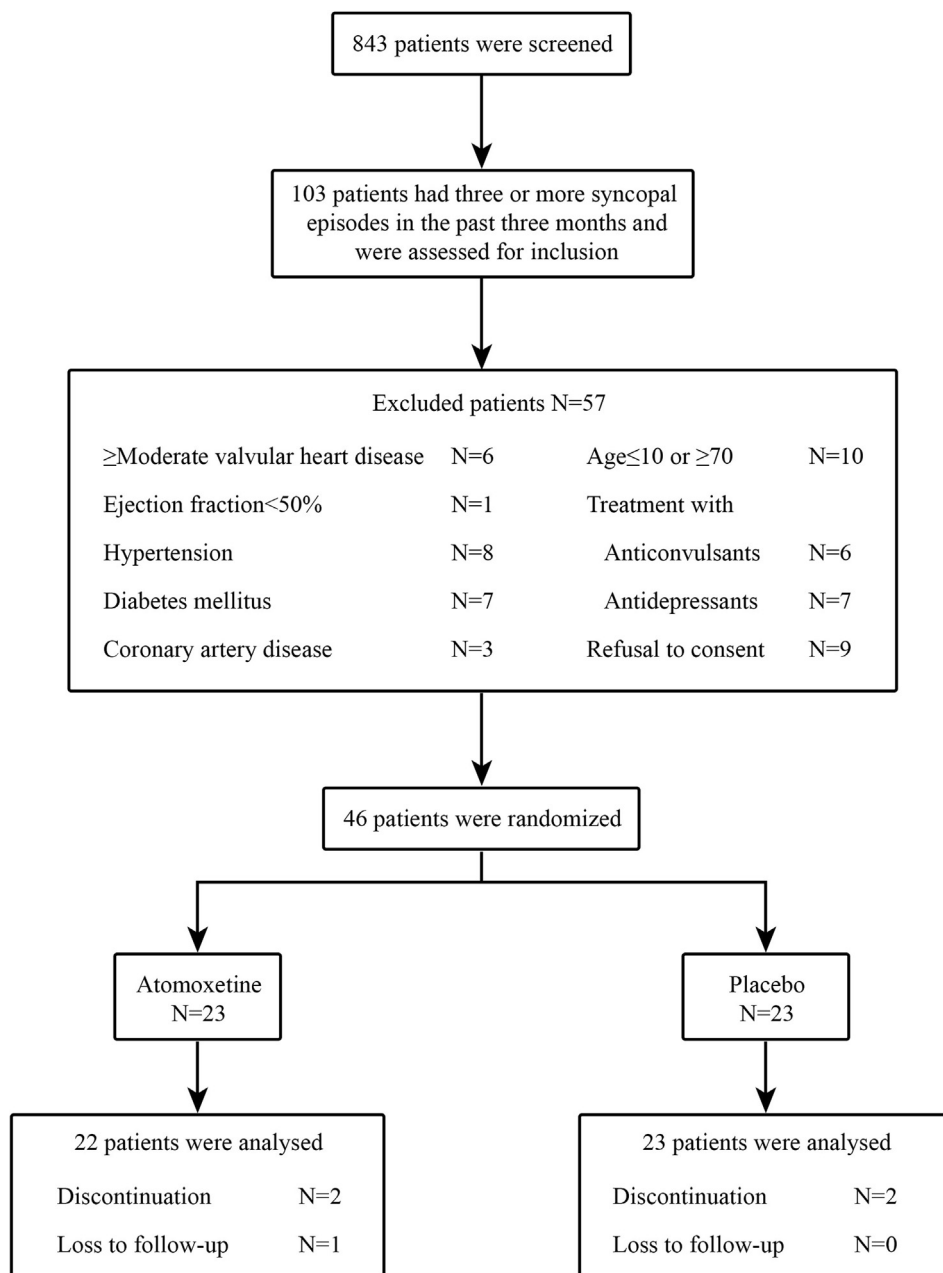
Fig. 1. Flow diagram of enrollment, randomization, and follow-up.

2.6. Sample size

Since this trial was designed and conducted as a pilot study, the sample size of 20 participants for each arm was adopted. A margin of 15% was considered to address potential missing data and loss to follow-up. Hence, 46 participants (23 in each group) were enrolled.

2.7. Statistical analysis

Essentially, we performed an intention-to-treat analysis, taking into account all the patients who were randomized initially, regardless of the course of treatment they went through. We would like to emphasize that a per-protocol analysis was also performed which demonstrated the same results, which was due to

the small number of patients who discontinued or were lost to follow-up.

To examine the difference in pre-syncope, syncope, and their composite by the intervention (atomoxetine versus placebo), the Mann-Whitney U test was conducted at one and three months separately. Time to the first recurrence was described using the Kaplan-Meier method and was compared between the two groups applying the log-rank test.

Patients' sex was reported as frequency and percentage. The normality of the continuous variables was assessed using skewness and kurtosis measures. The normally distributed variables were reported as mean with standard deviation. The skew distributed variables were reported as median with 25th and 75th percentiles. All statistical analyses were done applying IBM SPSS Statistics for Windows, version 23.0 (Armonk, NY: IBM Corp.).

Table 1
Baseline characteristics of patients.

Characteristic†	Atomoxetine N = 23	Placebo N = 23	P-value
Age (years)	34.0 ± 12.4	31.7 ± 13.8	0.553
Female sex	17 (73.9%)	15 (65.2%)	0.522
Weight (kg)	67.5 ± 14.2	63.3 ± 12.1	0.289
Systolic blood pressure (mmHg)	110 ± 17	111 ± 16	0.972
Diastolic blood pressure (mmHg)	71 ± 6	71 ± 9	0.954
Heart rate (beats/min)	73 ± 6	70 ± 7	0.852
Syncope history			
Syncopal episodes in the last 3 months	3.3 ± 0.7	3.3 ± 0.9	1.000
Pre-syncopal episodes in the last 3 months	5.6 ± 1.6	5.7 ± 1.4	0.848
Syncopal and pre-syncopal episodes in the last 3 months	8.8 ± 2.1	8.9 ± 2.1	0.889
Undergone HUTT	8 (34.8%)	9 (39.1%)	0.760
HUTT-Mixed response	1 (12.5%)	3 (33.3%)	0.658
HUTT-Cardio-inhibitory response	5 (62.5%)	5 (55.6%)	
HUTT-Vasodepressor response	2 (25.0%)	1 (11.1%)	
Family history of syncope	0 (0%)	2 (8.7%)	0.489
Family history of seizure	1 (4.3%)	0 (0%)	1.000
Family history of sudden cardiac death	0 (0%)	0 (0%)	–

†Data are reported as mean ± standard deviation or number (%). HUTT, head-up tilt test.

3. Results

3.1. Trial population

From July 2018 through July 2019, a total of 843 patients were screened, among whom 103 subjects fulfilled the enrollment criteria of at least three VVS episodes during the last three months. Another 57 patients were excluded for reasons detailed in Fig. 1. Eventually, 46 patients were randomly assigned to receive either atomoxetine or placebo. During follow-up, one patient withdrew from the study due to reluctance to continue participation. There were six patients (four in the placebo and two in the atomoxetine groups) under the age of 18 years. Since the starting dose of atomoxetine is 0.5 mg/kg/day which equals 20 mg for a 40-kg-individual [19], the lowest weight of our patients, we disregarded the weight-based dosing of atomoxetine. Verification of all outcomes was complete in 45 (97.8%) participants who were included in the intention-to-treat analysis. Demographic and clinical characteristics are summarized in Table 1.

3.2. Primary safety endpoint

Four patients experienced adverse events that resulted in discontinuation of atomoxetine (N = 2) and placebo (N = 2); all four cases occurred during the first two weeks (Fig. 1). In the atomoxetine arm, one patient experienced headache and another one felt nauseous. In the placebo group, discontinuation was due to

abdominal cramps in one case and shivering in the other one. These adverse events were self-limited and completely resolved after stopping the medications. All the other participants were able to follow through with the four-week regimen without any trouble.

3.3. Primary efficacy endpoint

Table 2 summarizes the recurrence of syncope and pre-syncope. During the first month of follow-up, the median [25th Percentile-75th Percentile] of the primary efficacy endpoint (syncope + pre-syncope) was 0 [0-1] in the atomoxetine arm as compared with 1 [0-1] in the placebo arm. In the first month, no patient experienced more than one episode of the primary efficacy endpoint at one month. The primary efficacy endpoint at three months of follow-up was 2 [2–2] in the atomoxetine arm as compared with 4 [3–5] in the placebo arm (Table 2). Compared to placebo, the reduction in the primary efficacy endpoint at one month with atomoxetine barely missed statistical significance ($P = 0.053$); however, atomoxetine significantly reduced the primary efficacy endpoint after three months ($P < 0.001$).

Considering syncopal episodes, there was no difference between the effects of atomoxetine and placebo after one or three months of follow-up (Table 2); however, the number of pre-syncopal episodes was significantly less frequent in the atomoxetine arm after the first and the third month of follow-up (Table 2). Moreover, in the atomoxetine arm, the median time to the first pre-syncopal episode was 55 days (95% confidence interval (CI): 41.21–68.79), while this was 27 days (95% CI: 14.48–39.52) for the placebo group ($P < 0.001$- Fig. 2). The syncope-free survival time was not different between study arms ($P = 0.903$), which may be attributed to the small number of syncopal episodes during the follow-up (Fig. 2).

3.4. Low blood pressure phenotype

The 2018 European Society of Cardiology syncope guidelines recommends pharmacologic therapy with fludrocortisone or midodrine in patients with VVS and a low blood pressure phenotype [2]. There is evidence of an association between chronic atomoxetine use and a rise in blood pressure [20]. In this regard, a subgroup analysis was performed among patients who had a baseline systolic blood pressure less than 110 mmHg (11 patients in the atomoxetine arm compared with 10 patients in the placebo arm). The primary efficacy endpoint, and the number of syncopal and pre-syncopal episodes of the patients with VVS and low blood pressure phenotype at one and three months were presented in Table 3. In this subgroup, the median of the primary efficacy endpoint was lower in the atomoxetine group compared to the placebo group. It should be noted that this difference was more pronounced in the number of pre-syncopal episodes rather than the number of syncopal episodes (Table 3). Median time to first pre-

Table 2
The rates of syncope and pre-syncope through follow-up.

Outcome†	One Month		P-value‡	Three Months		P-value‡
	Atomoxetine	Placebo		Atomoxetine	Placebo	
Number of syncopal and pre-syncopal episodes (The primary efficacy outcome)	0 [0-1] (0-1)	1 [0-1] (0-1)	0.053	2 [2-2] (1-7)	4 [3-5] (3-11)	<0.001
Number of syncopal episodes	0 [0-0] (0-1)	0 [0-0] (0-1)	0.975	0 [0-1] (0-3)	0 [0-1] (0-3)	0.914
Number of pre-syncopal episodes	0 [0-1] (0-1)	1 [0-1] (0-1)	0.05	2 [1-2] (1-4)	4 [3-4] (2-8)	<0.001

†Data are reported as median [25th Percentile-75th Percentile] and (Minimum-Maximum).
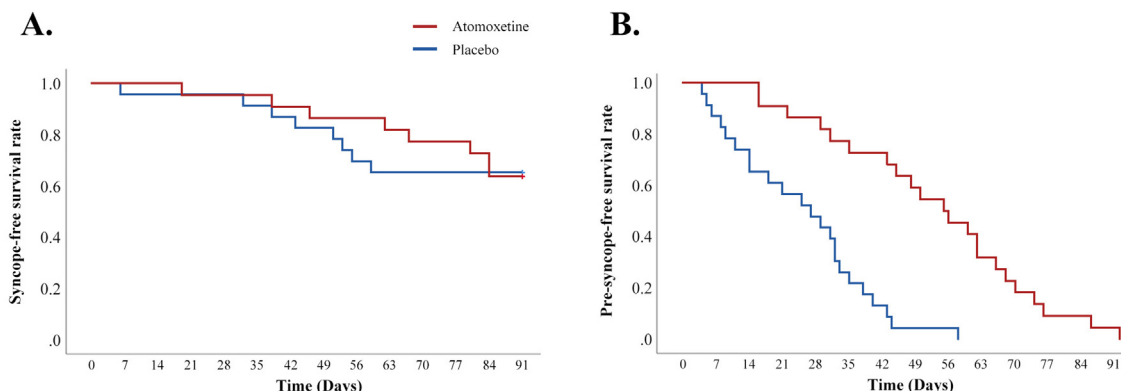‡ Mann-Whitney U Test.

Fig. 2. Total population: **A.** Syncope-free survival, **B.** Pre-syncope-free survival.

Table 3
The rates of syncope and pre-syncope of patients with low blood pressure phenotype through follow-up.

Outcome†	One Month		Three Months	
	Atomoxetine	Placebo	Atomoxetine	Placebo
Number of syncopal and pre-syncopal episodes (The primary efficacy outcome)	0 [0-0] (0-1)	1 [0-1] (0-1)	2 [1-2] (1-3)	5 [5-5] (4-11)
Number of syncopal episodes	0 [0-0] (0-0)	0 [0-0] (0-1)	0 [0-0] (0-0)	1 [0-1] (0-3)
Number of pre-syncopal episodes	0 [0-0] (0-1)	1 [0-1] (0-1)	2 [1-2] (1-3)	4 [4-5] (4-8)

†Data are reported as median [25th Percentile-75th Percentile] and (Minimum-Maximum).

syncopal attack was 56 days in the atomoxetine group as opposed to 9 days in the placebo group.

4. Discussion

In this double-blind placebo-controlled randomized clinical trial, we found that in patients with recurrent VVS, atomoxetine was associated with a borderline not-significant lower number of combined syncopal and pre-syncopal episodes at one month. The exploratory analysis showed remarkable reduction in this endpoint at three months; nonetheless, syncopal episodes did not show a significant difference. Furthermore, we found that among patients with a baseline systolic blood pressure less than 110 mmHg, both syncope- and pre-syncope-free survival were significantly greater in the atomoxetine arm.

4.1. Sympathetic nervous system and vasovagal reflex

In a healthy individual, standing results in the accumulation of blood in the veins of the lower limbs according to the gravitational force. Consequently, arterial baroreceptors sense this displacement as reduced blood pressure and in turn, send signals to stimulate the sympathetic nervous system (SNS). Activation of the SNS causes increased systemic vascular resistance and heart rate, which results in the maintenance of blood pressure and also blood flow to the brain [21]. It is hypothesized that impairment in this natural reflex may be responsible for VVS. Vaddadi and colleagues [7] evaluated this hypothesis if SNS dysfunction predisposes individuals to VVS. They studied SNS function in 36 patients with VVS and 18 healthy persons. They categorized patients with VVS based on the baseline systolic blood pressure, 21 normotensive-(>100 mmH

g) and 15 hypotensive-(≤100 mmHg) patients. They investigated the SNS at three levels of muscle sympathetic nerve activity (MSNA), norepinephrine spillover, and sympathetic nerve proteins. During HUTT, normotensive patients showed a normal increase in MSNA, no increase in norepinephrine spillover at all, normal tyrosine hydroxylase (TH) levels, and increased NET levels. This is while hypotensive patients demonstrated a two-fold increase in MSNA, reduced norepinephrine spillover, and low TH and NET levels. Therefore, patients with VVS have reduced norepinephrine spillover in response to HUTT with different mechanisms: 1) Increased NET levels in normotensive-patients lead to intensified reuptake of norepinephrine, reduced norepinephrine spillover, and blunted SNS response to standing. 2) Low TH levels in hypotensive-patients are the cause of diminished production of norepinephrine and consequent reduced norepinephrine spillover. It seems that low NET levels are a compensatory response to the reduced production of norepinephrine in this subset of patients. In summary, their study suggests that reduced norepinephrine spillover is a therapeutic target in patients with VVS which we can address by NET inhibition in normotensive- or augmentation of norepinephrine synthesis in hypotensive-patients; nonetheless, NET inhibition increases norepinephrine spillover in both subsets of patients, hypothetically [7]. This approach seems right theoretically according to the above-mentioned mechanism; however, it should be noted that this mechanism is one amongst many and the exact pathophysiological mechanism of VVS is not defined yet.

4.2. NET inhibition in patients with VVS

Although there is evidence in favor of pathophysiological benefits of NET inhibition in VVS, there are few clinical studies in this

regard [9,10]. Sheldon et al. [9] reported clinical benefit of sibu-tramine, a NE and serotonin reuptake inhibitor, in 7 patients with highly recurrent VVS who did not respond to several treatments. They found that daily usage of 15 mg of sibutramine is well toler-ated and causes a 94% reduction of events in responders (5 patients with >50% reduction in the frequency of episodes) [9]. In a proof of principle study, they studied 56 patients with VVS who had three spells in the last year. They received either two doses of atomox-etine 40 mg (N = 29) or two doses of placebo (N = 27) in a random-ized fashion followed by a 60-minute drug-free HUTT. Patients in the placebo group were more likely to have syncope (70% versus 34%; P = 0.003); however, patients who received atomoxetine experienced isolated pre-syncope more frequently (45% versus 7%; P = not reported). Given that the composite of pre-syncope and syncope was not statistically different across the groups (79% versus 78% in the atomoxetine and the placebo group, respec-tively; P = 1.0), the authors concluded that although atomoxetine failed to avert the vasovagal reflex, it successfully prevented the evolution of pre-syncope to syncope [10]. In our study, we con-firmed that atomoxetine has beneficial effects on the recurrence of spells in patients with VVS; nevertheless, we found that atomox-etine aborted pre-syncopal episodes more than syncopal episodes. Moreover, in contrast with Sheldon et al. [10], we found a lower number of combined syncopal and pre-syncopal episodes in the atomoxetine arm than the placebo group. This discrepancy may be attributed to several aspects: 1) Our patients had at least three syncopal episodes in the last three months, while their patients had three syncopal episodes in the last year [10]. Hence, our patients were generally sicker. 2) In the Sheldon et al. [10] study, patients received 80 mg of atomoxetine for a day; however, our patients were given 20 mg daily for two weeks followed by 40 mg daily for another two weeks. 3) The last but not the least dif-ference is that we followed patients for real-life recurrence of VVS while they evaluated HUTT-induced VVS [10]. False-positive and false-negative results of HUTT underscore the difference between the aforementioned outcomes [22–24]. Furthermore, it should be noted that our failure to show beneficial effects of atomoxetine on the recurrence of syncope may be attributed to the short dura-tion of follow-up, a small number of syncopal episodes, and admin-istration of low dose atomoxetine.

In this pilot study, a high prevalence of poor and intermediate metabolizers of atomoxetine in the Iranian population [17,18] hin-dered us from administering higher doses of atomoxetine. More-over, we did not extend the duration of administration of atomoxetine due to concerns of adverse events in our patients and ethical considerations. In the treatment of patients with attention-deficit hyperactivity disorder with atomoxetine, studies suggest that atomoxetine may have long-lasting effects, even after its discontinuation, probably through neuroadaptive changes [19]. Although its plasma half-life is about 5 h, its once-daily dosing has been proven to be effective. Furthermore, patients maintain their response for several months after discontinuation of atomoxetine [19]. According to our results, we hypothesize that there might be a delayed effect with atomoxetine in patients with VVS; nonetheless, future research is required to investigate this specula-tion as the mechanism of action of atomoxetine in preventing syn-cope. Moreover, our promising results may permit us to up-titrate the atomoxetine dose in Iranian patients in future studies.

In our investigation, a subgroup of patients with a baseline sys-tolic blood pressure measurement less than 110 mmHg showed lowered recurrences of both syncope and pre-syncope. Such obser-vation among the hypotensive patients, although not solid due to the pilot nature of this study, could be attributable to the long-term effects of atomoxetine on blood pressure [20]. It should be noted that there might be a difference between the short and long-term effects of atomoxetine on the cardiovascular system.

In the study by Sheldon et al. [10] atomoxetine was demonstrated to exert its influence due to an increased heart rate. On the other hand, increased blood pressure is a known effect of atomoxetine with its long-term use [20]. In any case, discussing the exact hemo-dynamic changes with atomoxetine is beyond the scope of this study and future research is required to investigate its efficacy in patients with VVS.

4.3. The placebo effect in patients with VVS

Noticeably, all of our patients experienced a reduction in the primary endpoint after the third month of follow-up compared to their baseline regardless of the treatment. In addition to the patient education recommendations including non-pharmacological measures [1,2], the regression toward the mean, high remission rates of VVS [25], and the placebo effect may con-tribute to this reduction [26]. In a comprehensive review article, Sahota and colleagues [26] elaborated on the substantial role of placebo type and also the effect of expectancy in symptom reduc-tion in patients with VVS. In the Prevention of Syncope Trial (POST), Sheldon et al. [27] found that 60% of patients who received a placebo did not experience syncope in the follow-up year. Fur-thermore, Ammirati and colleagues [28] compared the efficacy of beta-blocker treatment (non-invasive) versus permanent cardiac pacing treatment (invasive) in patients with VVS. Although both treatments were shown to have little or no clinically significant benefits later in placebo-controlled randomized trials, authors observed that the invasive treatment/placebo resulted in better outcomes compared with the non-invasive treatment/placebo [28]. In our study, two patients in the placebo arm incurred irrele-vant side effects, which may be compatible with the placebo effect in these patients.

4.4. Limitations

Although this is a double-blind placebo-controlled randomized clinical trial, it can be improved by addressing some limitations. First, since this was a pilot study, the results cannot be deemed conclusive. Future studies would need a larger sample size, an extended duration of treatment, and a longer duration of follow-up; nevertheless, this is a pilot study to introduce the hypothesis that atomoxetine indicates promising results for patients with VVS. Considering the small range of pharmacologic options and the currently insufficient evidence regarding the treatment of VVS, along with the novelty of our study in evaluating clinical out-comes in a highly symptomatic group of patients, we would imag-ine that the sample size and follow-up duration should not be considered as major flaws. Second, due to the absence of evidence regarding dosage and treatment duration of atomoxetine in patients with VVS, we could not administer its maximum tolerated dose. Third, the selected population may not be representative of all patients with VVS since the patients included in this study had highly recurrent VVS. Ultimately, we advise caution in inter-preting the results of this preliminary study until further evidence becomes available on this matter.

4.5. Future studies

We reported primary efficacy and safety endpoints in this ran-domized controlled trial and also presented a subgroup analysis; nonetheless, this is a pilot study which mainly delineates the fea-sibility of a larger study [29,30]. Despite the high prevalence of poor/intermediate atomoxetine metabolizers in Iran, Iranian patients well tolerated 40 mg of daily atomoxetine. Hence, we may increase the dosage of atomoxetine in future studies due to its tolerability profile among poor/intermediate metabolizers.

Given the lowest weight of 40 kg in our patients, we disregarded the weight-based regimen of atomoxetine in our study; however, it should be noted in future studies on pediatric patients with lower weights. We included patients with highly recurrent VVS to capture a reasonable number of primary endpoints in the short duration of follow-up of this study; nevertheless, future studies should include more representative sample of patients with VVS with a more prolonged duration of follow-up. Additionally, the low blood pressure phenotype subgroup of patients with VVS may warrant specific consideration due to our findings in future studies.

5. Conclusions

To the best of our knowledge, this is the first clinical trial focusing on the efficacy of atomoxetine in preventing syncopal and pre-syncopal episodes in real life. We found that one-month treatment with atomoxetine led to a significant reduction in the composite of syncopal and pre-syncopal episodes at three months, but not at one month. In patients with low blood pressure, atomoxetine use was associated with a lower number of syncopal and pre-syncopal episodes after one and three months. This pilot study may provide the basis for the development of future large randomized trials regarding the efficacy and safety of atomoxetine in VVS.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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