Atomoxetine in patients with recurrent vasovagal syncope for preventing vasovagal attacks and improvement of depression and anxiety: a randomized double-blind placebo-controlled clinical trial

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Background: Studies showed that sibutramine or reboxetine reduced head-up tilt (HUT)-induced syncope and pre-syncope by 78%. Furthermore, in an open-label series of highly symptomatic patients with vasovagal syncope (VVS), sibutramine reduced frequency of vasovagal spells. In a recent proof of principle study, atomoxetine reduced number of HUT-induced syncopal episodes by about 50% compared to placebo.

Purpose: In this study, we aimed to evaluate the effectiveness of atomoxetine on preventing recurrence of syncopal and pre-syncopal episodes in patients with recurrent VVS after three months of follow-up. Moreover, we determined whether it can improve patients' anxiety and depression.

Methods: In this double-blind placebo-controlled randomized clinical trial, we screened 843 patients with VVS. Patients with $10 < \text{age} < 70$ years who had ≥ 3 syncopal episodes in the past three months were included. Eventually, 46 patients were randomized to receive atomoxetine (20 mg daily for two weeks followed by 40 mg daily for two weeks, N=23) or placebo (for four weeks, N=23). The primary endpoint was the number of syncopal and pre-syncopal episodes at one and three months and was analyzed by the repeated measures analysis of variance. Secondary endpoints were decrements of depression and anxiety measured by the Hospital Anxiety and Depression Scale after three months and were analyzed by the Mann-Whitney U test.

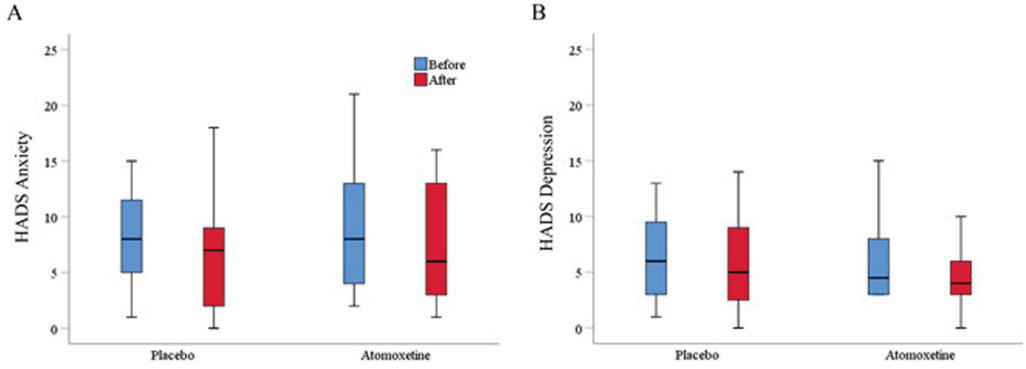
Results: The primary endpoint was lower after three months in the atomoxetine arm (2.3±1.3 vs 4.3±1.7), with a significant between-subjects effect by atomoxetine versus placebo ($P<0.001$). This observation was primarily due to the reduction of pre-syncopal episodes rather than syncopal episodes ($P<0.001$ vs $P=0.944$, respectively, Table). In contrast with placebo, atomoxetine significantly improved anxiety ($P=0.048$ vs $P=0.352$) and depression ($P=0.001$ vs $P=0.206$) after three months; nonetheless, anxiety and depression scores of the patients were not different across the groups after three months ($P>0.05$, Figure).

Conclusions: In patients with VVS, atomoxetine significantly reduced the recurrence of a composite of syncopal and pre-syncopal episodes, and remarkably improved anxiety and depression at three months.

The rates of syncope and pre-syncope

Outcome*	Atomoxetine		Placebo		P value‡
	1 month	3 months	1 month	3 months	
Number of syncopal episodes	0.05±0.2	0.5±0.7	0.04±0.2	0.4±0.7	0.944
Number of pre-syncopal episodes	0.3±0.5	1.8±0.9	0.6±0.5	3.9±1.2	<0.001
Number of syncopal and pre-syncopal episodes	0.4±0.5	2.3±1.3	0.6±0.5	4.3±1.7	<0.001

*Data are reported as mean ± standard deviation. ‡Between-subjects effects adjusted for baseline measures in repeated measures ANOVA.



Anxiety and Depression of the Patients