

Effects of citalopram on heart rate variability in women with generalized anxiety disorder

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Original Article

Abstract

BACKGROUND: Heart rate variability (HRV) is defined as variations in R-R interval with time. Dysautonomia is common in patients with psychiatric disorders such as depression and anxiety. Using HRV analysis, recent studies showed that in anxiety disorders, the vagal cardiac function decreases, and sympathetic function increases. This study aimed at investigating citalopram effects on HRV.

METHODS: This before and after study was conducted in 25 generalized anxiety disorder (GAD) patients. GAD was diagnosed based on clinical interview according to diagnostic and statistical manual of mental disorders IV-Text revised (DSM-IV-TR) criteria using Structured Clinical Interview for DSM Disorders-I questionnaire. A cardiologist studied 24 h ambulatory monitoring of the electrocardiogram (Holter) on all patients before the treatment. A volume of 20 mg of citalopram was administered to the subjects on a daily basis. Then, they were studied by Holter monitoring again after 1-month of administration of citalopram.

RESULTS: The average age of participants was 35.32 ± 8.7 . The average Holter monitoring time was 23.29 ± 1.14 h before treatment and 23.81 ± 0.68 after it. The 3 h low frequency/high frequency ratio was significantly different between 3 h segments of time before treatment ($P < 0.001$). This difference was even higher after treatment ($P = 0.001$). Data showed an increase in parasympathetic tone during sleep both before and after treatment.

CONCLUSION: These patients showed some impairments of HRV indices that did not improve by citalopram in future, the clinical importance of such disturbances should be evaluated in details with prolonged follow-up and greater sample size.

Keywords: Anxiety Disorders, Heart Rate, Ambulatory Electrocardiography

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Introduction

Heart rate variability (HRV) is defined as variations in R-R interval with time. HRV is actually heartbeat variations from one beat to another, which is used for evaluation of sympathetic and vagus nerve effects on the Sinoatrial node, and consequently on the heartbeat.^{1,2}

Apart from body mass index and elevated blood glucose or blood pressure, mental status, and related processes can significantly affect cardiac autonomic control.³ Stressors increase cardiac sympathetic control and decrease cardiac parasympathetic control, which consequently result in an increase in low frequency (LF) HRV and a decrease in high

frequency (HF) HRV.⁴ Dysautonomia is common in patients with psychiatric disorders such as depression and anxiety. This is diagnosed via HRV.⁵ Anxiety disorders are highly associated with dysautonomia, which increases cardiovascular mortality. Patients with panic disorder or phobia are prone to cardiovascular diseases.⁶⁻⁸ Using HRV analysis, recent studies showed that in anxiety disorders, the vagal cardiac function decreases, and sympathetic function increases.^{9,10} Miu et al. showed a correlation between characteristic anxiety and dysautonomia using HRV analysis.¹¹

Generalized anxiety disorder (GAD) is characterized by a pattern of frequent, persistent

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worry, and anxiety that is disproportionate to the impact of the events or circumstances on which the worry focuses.¹² An acute episode of anxiety is defined as an increase in heart rate, decrease in HRV, and respiratory sinus arrhythmia. Anxiety disorders are highly associated with an increased risk of mortality and cardiovascular complications.^{13,14} One of the hypotheses raised on this issue is impaired regulation of cardiac autonomic control due to the correlation of the cardiac autonomic control system with cardiovascular diseases and mortality.¹⁵

The selective serotonin reuptake inhibitors (SSRIs) do have cardiac effects, the best demonstrated of those being a mild bradycardia observed during chronic treatment with fluoxetine, fluvoxamin, and paroxetine. Moreover, there are increasing the number of case reports on dysrhythmia and syncope associated with fluoxetine and another SSRIs treatment and overdose. A multicenter case-control study has shown that in the elderly the consumption of fluoxetine was significantly associated with an excess risk of syncope and orthostatic hypotension.¹⁶ This study aimed to investigate effects of citalopram on HRV.

Materials and Methods

This before and after study aimed to investigate the effects of citalopram on HRV in patients with GAD. GAD was diagnosed based on clinical interview, according to diagnostic and statistical manual of mental disorders IV–Text revised criteria using Structured Clinical Interview for DSM Disorders-I questionnaire.¹² Due to shortage in studies that could provide valid data to estimate the sample size appropriately, we were not able to make a sample size calculation and started the study as a pilot exploratory design with minimum sample size (30 patients). Because of a higher prevalence of GAD in women, all of the participants were selected by using convenience sampling from female patients. Patients from Razi Hospital, Tabriz, Iran, outpatient clinic voluntarily entered the study after being diagnosed with GAD and considering inclusion and exclusion criteria from August to December in 2013. After explaining the safety of Holter monitoring to patients, providing them with the full information required for participation in interventional studies and letting them know that no cost will be imposed on them, subjects entered the study. In addition, all of them could withdraw from the study at any point. They were also ensured that all of their personal and

medical information would remain confidential.

A cardiologist performed 24 h ambulatory monitoring of the electrocardiogram (Holter–Norav version 2.978) on all patients before the treatment. A volume of 20 mg of citalopram was administered to the subjects on a daily basis. Then, they were studied by Holter monitoring again after 1-month of administration of citalopram. Usually, the patients with GAD show a response to treatment in 4 weeks.

Techniques for measures calculating HRV in regard of equipment, condition, and preparation met the criteria mentioned in another article on HRV.¹⁷

Holter monitoring calculates two indicator categories HRV: Time domain and frequency domain parameters. Frequency domain analysis is measured in 2-5 min intervals. HRV indicators are presented in table 1. The 24 h monitoring of HRV are divided into 4 periods of 3 h recordings by the device (16-19, 20-23, 02-05 and 11-14). Each parameter of time domain and frequency domain measured again. Inclusion criteria were female gender, diagnosed with GAD and informed consent to participate in the study. Exclusion criteria were pregnant and lactating women, menopausal age, having an underlying heart disease, medical conditions affecting the heart rhythm including thyroid disease, diabetes mellitus, neuropathy, and tetraplegia concurrent use of drugs affecting heart rhythm and existence of atrial fibrillation; and significant rhythm disorders of heart like as frequent extra stimuli. Demographic variables that were assessed in the study were: Age, education level, and occupation. GAD diagnosis was given if at least three symptoms were present.

Descriptive methodologies (frequency, percentage, mean \pm standard deviation) were used to perform statistical analysis. Kolmogorov–Smirnov test was used for normality assessment. In variables that had non-normal distribution, we used non-parametric tests (Wilcoxon test) to perform comparisons between before and after HRV indices in variables with normal distribution, paired t-test was used. Used repeated measure analysis of variance for evaluates, the effect of 3 h segments of time (within subjects) and groups (between subjects). Mauchly's sphericity test was used to validate it. If sphericity is violated, the Greenhouse–Geisser correction was used. All statistical analyses were conducted via SPSS software for Windows (version 16, SPSS Inc., Chicago, IL, USA). Significance level was considered as $P < 0.050$. Trends for time domain measures in 24 hour electrocardiography monitoring are shown in figure 1.

Results

The average age of participants was 35.32 ± 8.7 , with the minimum and maximum age of 25 and 59, respectively. Five patients dropped out of the study (because of unwillingness to do after treatment Holter monitoring), so 25 were studied. Four patients (16%) were single, and 21 of them (84%) were married. In addition, 6 (24%), 11 (44%), and 8 (32%) held undergraduate, graduated, and higher education degrees, respectively. Seven (28%) and 18 (72%) were employed and housekeepers, respectively. The average Holter monitoring time was 23.29 ± 1.14 h before treatment and 23.81 ± 0.68 after it table 2 shows the variation of HRV indices in 24 h.

The data showed that 7 individuals suffered from ventricular arrhythmia before the administration of citalopram. Moreover, 3, 2, and 2 patients suffered from premature ventricular contraction (PVC), bigeminy and trigeminy, respectively. In follow-up, Holter monitoring, which was done 1-month after the administration of

citalopram, ventricular arrhythmia, PVC, bigeminy, and trigeminy were observed in 5, 2, 2, and 3 individuals, respectively. One of the three patients suffering from PVC prior to the treatment had no symptoms. The frequency of PVCs in the other 2 participants reduced from 818 to 618 in the first and from 1050 to 625 beats in the second patient, during 24 h, respectively. During the initial monitoring, supraventricular arrhythmia (SVT) [premature atrial contraction (PAC)] was observed in 4 cases and SVT in one case, while during the follow-up monitoring, PAC was observed in 3 cases. The frequency of PACs increased in one case after treatment, but none of the subjects had SVT.

The 3 h LF/HF ratio was significantly different between 3 h segments of time before treatment ($P < 0.001$). This difference was higher after treatment ($P = 0.001$) (Figure 2). Figure 2 shows a significant increase in parasympathetic tone during sleep both before and after treatment. Table 3 shows no significant different between variables before and after using citalopram.

Table 1. Heart rate variability (HRV) parameters: Definition and normal ranges

Variables	Definition	Normal values (mean \pm SD)
Time domain		
SDNN (ms)	Standard deviation of NN intervals (24 h)	141.0 ± 39.0
SDANN (ms)	Standard deviation of average (5 min duration) of NN interval	127.0 ± 35.0
RMSSD (ms)	Square root of mean squared difference of successive NN intervals	27.0 ± 12.0
HRV triangle (ms)	Heart rate variability	37.0 ± 15.0
Frequency domain		
ULF(ms^2)	Ultra low frequency	1170.0 ± 416.0
VLF (ms^2)	Very low frequency	975.0 ± 203.0
LF (nu)	Low frequency	54.0 ± 4.0
HF (nu)	High frequency	29.0 ± 3.0
LF/HF ratio		1.5 ± 2.0

SD: Standard deviation; SDNN: Standard deviation of NN intervals; SDANN: Standard deviation of average of NN interval; RMSSD: Root of mean squared difference of successive NN intervals; HRV: Heart rate variability; ULF: Ultra low frequency; VLF: Very low frequency; LF: Low frequency, HF: High frequency

Table 2. Heart rate variability (HRV) in 24 h Holter monitoring before and after citalopram

HRV	Parameters		
	Before	After	P
Time domain			
SDNN	252.0 ± 207.0	317.0 ± 378.0	0.354*
SDANN	121.0 ± 88.0	118.0 ± 78.0	0.664
RMSSD	248.0 ± 314.0	316.0 ± 496.0	0.440*
HRV triangle	36.5 ± 9.2	37.5 ± 9.2	0.821
Frequency domain			
ULF	90.0 ± 300.0	93.0 ± 33.0	0.543
VLF	261.0 ± 68.0	254.0 ± 64.0	0.876
LF	154.0 ± 29.0	151.0 ± 21.0	0.305
HF	137.0 ± 33.0	136.0 ± 33.0	0.848
LF/HF	1.2 ± 0.5	1.2 ± 0.4	0.582

* Wilcoxon test; Other variables: paired t-test; SDNN: Standard deviation of NN intervals; SDANN: Standard deviation of average of NN interval; RMSSD: Root of mean squared difference of successive NN intervals; HRV: Heart rate variability; ULF: Ultra low frequency; LF: Low frequency, HF: High frequency; VLF: Very low frequency

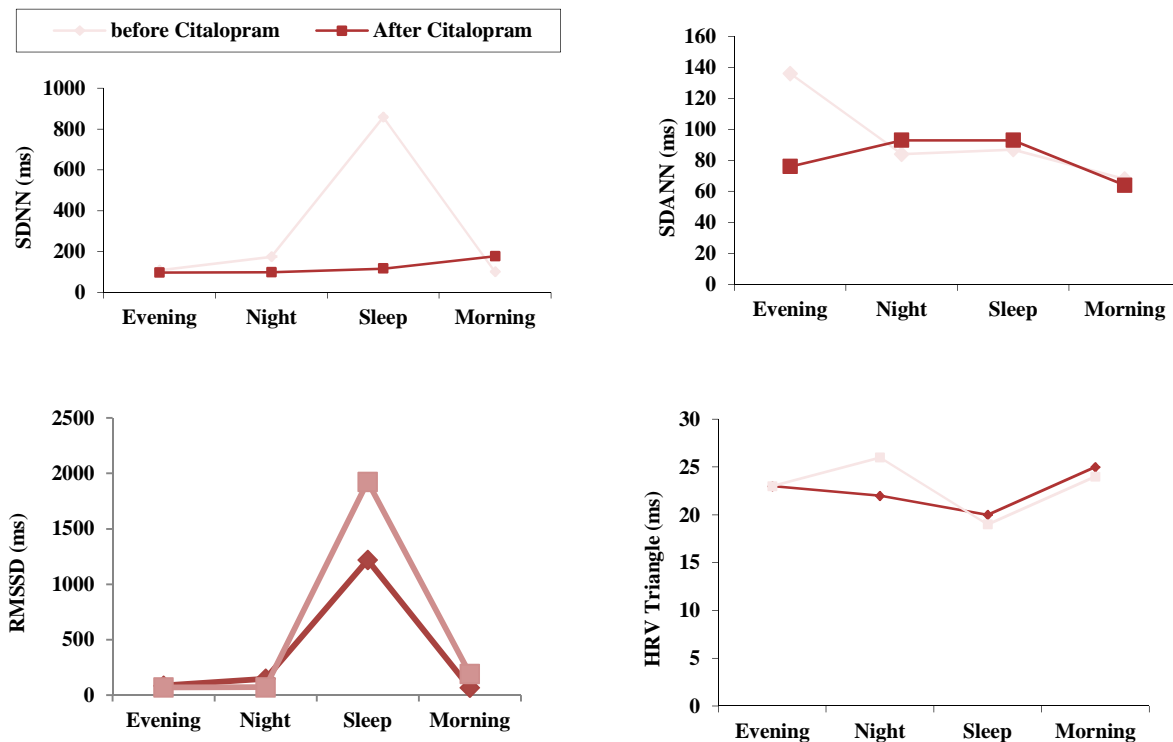


Figure 1. Trends of time domain measures in 24 h electrocardiogram monitoring

SDNN: Standard deviation of NN intervals; SDANN: Standard deviation of average of NN interval; RMSSD: Root of mean squared difference of successive NN intervals; HRV: Heart rate variability

In frequency domain analysis, LF/HF ratio variations, which is a sign of sympathetic and parasympathetic balance, were compared during 3-h periods before the treatment, and indicated a significant difference ($P = 0.010$). This index showed that sympathetic and parasympathetic balance differences during different periods of the day were different between time periods, but this difference was higher after treatment ($P = 0.003$). These findings mean that the flat and narrow difference of balance between sympathetic and parasympathetic activation becomes wider after therapy. While the sympathetic tone of patients decreased after treatment but the parasympathetic tone was not increased significantly after treatment. Sleep is the time that increasing in parasympathetic tone should be increased but both before and after treatment this increase was not high enough to improve the LF/HF ratio.

Discussion

HRV triangle is the estimate for total HR variability. This index was 36.52 before treatment, which increased to 37.55 after treatment. Although this difference was not different statistically, but the difference between time segments of HRV before treatment was significant ($P = 0.010$). This difference was not significant after treatment, which indicates

some kind of autonomic stability after therapy with citalopram.

The standard deviation of NN intervals (SDNN) is an estimate for total HRV parameters. The total value of this parameter was 252 and the normal value 141. The average is better than normal but when comparing 3 h periods, the privilege of this parameter occurred during sleep. In other words, when the patient was awake this parameter was lower than normal. Furthermore, van Zyl et al. showed that SSRIs decrease heart rate and also cause a possible increase in SDNN.¹⁸

The disturbances in autonomic function were high when the patient was awake. It is notable that standard deviation of average of NN interval (SDANN) before treatment was very high when Holter monitoring started during evening and soon reached its average state during night time. This finding did not occur during follow-up. This finding may be related to the extra anxiety of patients who were attached to leads and device for the first time.

SDANN, which is a long-term estimate of HRV, may be a better estimation for HRV because it removes short-term effects of HRV components. This parameter was always lower in patients before and after treatment. Patients with anxiety disorders had autonomic disorders, which did not improve by citalopram administration despite the improvement in their clinical status.

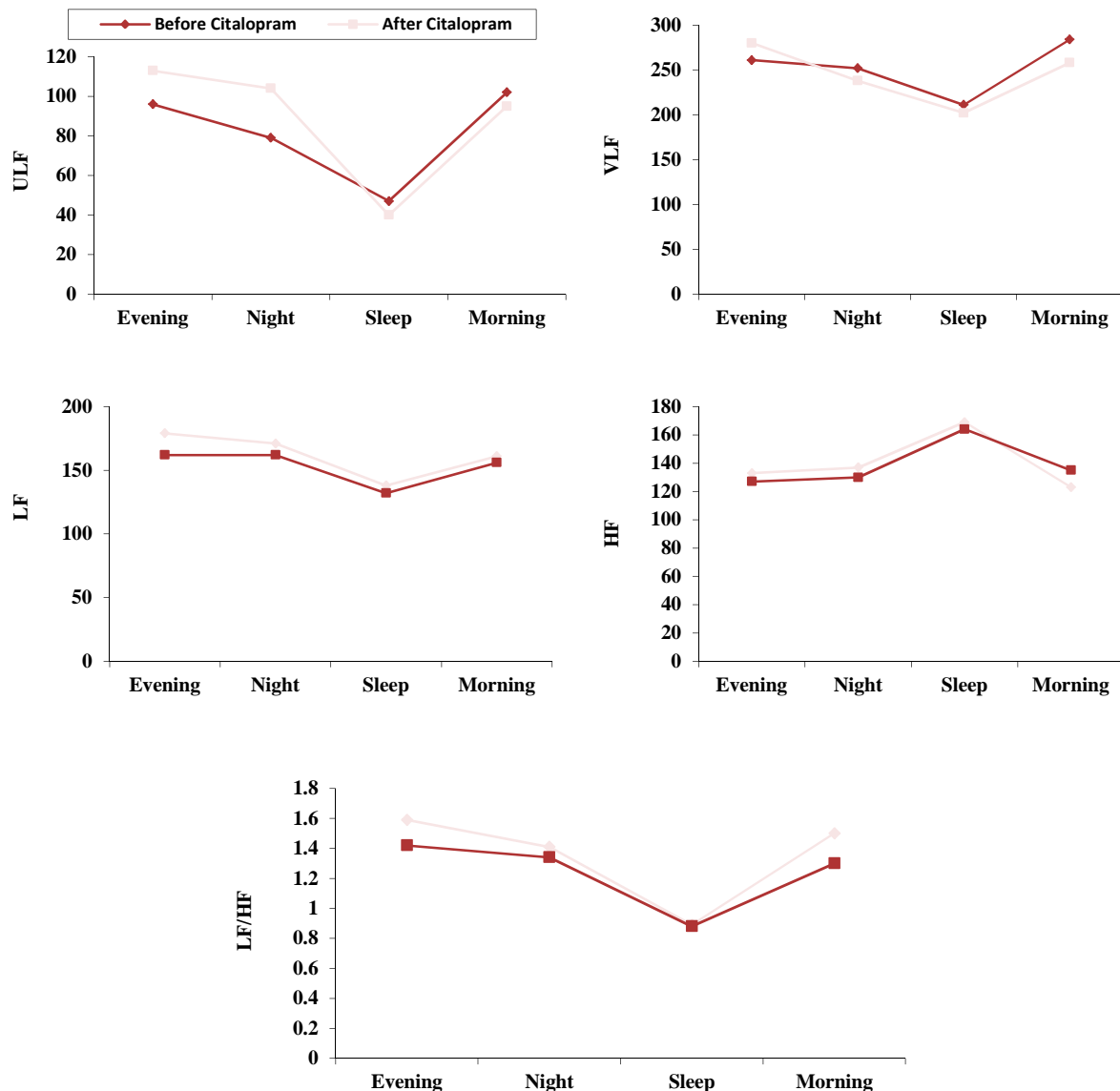


Figure 2. Trends of frequency domain measures in 24 h electrocardiogram monitoring
ULF: Ultra low frequency; VLF: Very low frequency; LF: Low frequency, HF: High frequency

Root mean square of the successive differences is an estimate of short-term variation of autonomic balance. This parameter was always higher than normal value, which indicates a high level of fluctuation and variation in the autonomic drive of patients. The clinical importance of this finding should be evaluated further.

The value of LF and HF in the frequency domain analysis was lower than normal before and after therapy. The ratio of LF/HF was higher than normal values except during sleep. This finding is not a correct finding and is could not be interpreted as a sign of improvement in HRV. The values of LF and HF were less than normal. Their ratio can be normal but based on components of this ratio, the

LF/HF ration cannot be interpreted as a sign of improvement in HRV. Actually, this finding shows our patients had blunted autonomic status before and after therapy for anxiety disorders.

The above mentioned results are comparable with other findings. McFarlane et al. showed that the HRV improvement indices in depressed patients with myocardial infarction, who received sertraline for 6 months was more than those of the control group, and this increase in HRV was equal to non-depressed patients.¹⁹ In a randomized clinical trial study, Brunoni et al. demonstrates that HRV did not change after treatment with 50 mg sertraline for 6 weeks, neither was an increased HRV observed in the clinical response.²⁰

Table 3. Heart rate variability (HRV) in four periods of 3 h before and after citalopram

HRV	Before citalopram					After citalopram					P*
	Evening	Night	Sleep	Mid-day	P	Evening	Night	Sleep	Mid-day	P	
Time domain											
SDNN	108 ± 49	174.0 ± 356.0	858.0 ± 3303.0	100.0 ± 30.0	0.352	96 ± 28	98.0 ± 29.0	116.0 ± 78.0	176.0 ± 354.0	0.326	0.337
SDANN	136 ± 133	84.0 ± 91.0	87.0 ± 72.0	68.0 ± 82.0	0.150	76 ± 88	93.0 ± 81.0	93.0 ± 104.0	64.0 ± 53.0	0.298	0.505
RMSSD	86 ± 79	148.0 ± 364.0	1219.0 ± 4920.0	67.0 ± 39.0	0.335	70 ± 45	71.0 ± 39.0	1926.0 ± 6998.0	193.0 ± 526.0	0.261	0.730
HRV triangle	23 ± 7	22.4 ± 5.6	20.3 ± 5.2	25.8 ± 9.3	0.032	23 ± 6	25.9 ± 7.6	19.4 ± 9.1	24.1 ± 5.5	0.777	0.767
Frequency domain											
ULF	96 ± 50	76.0 ± 42.0	47.0 ± 26.0	102.0 ± 44.0	0.840	113 ± 48	104.0 ± 43.0	40.0 ± 22.0	95.0 ± 50.0	0.026	0.213
VLF	261 ± 95	252.0 ± 86.0	211.0 ± 75.0	284.0 ± 85.0	0.515	280 ± 76	238.0 ± 77.0	202.0 ± 29.0	258.0 ± 87.0	0.132	0.548
LF	179 ± 54	171.0 ± 44.0	138.0 ± 31.0	161.0 ± 43.0	0.015	162 ± 47	162.0 ± 35.0	132.0 ± 29.0	156.0 ± 32.0	0.009	0.124
HF	133 ± 47	137.0 ± 41.0	169.0 ± 43.0	123.0 ± 46.0	0.959	127 ± 42	130.0 ± 37.0	164.0 ± 42.0	135.0 ± 43.0	<0.001	0.859

Use repeated measure analysis of variance; * Significant between the average of variable before and after using citalopram; SDNN: Standard deviation of NN intervals; SDANN: Standard deviation of average of NN interval; RMSSD: Root of mean squared difference of successive NN intervals; HRV: Heart rate variability; ULF: Ultra low frequency; LF: Low frequency; HF: High frequency; VLF: Very low frequency

In their clinical trial study, Chappell et al. stated that duloxetine and escitalopram did not have a significant effect on HRV.²¹ Penttila et al. reported that the cardiac effect of citalopram on heart rate was the same as a placebo.²² In the Netherlands Study of Depression and Anxiety, Licht et al. showed that patients with anxiety had lower SDNN compared to the control group.²³ Kemp et al. in a meta-analysis showed that tricyclic medication decreased HRV, although serotonin reuptake inhibitors, mirtazapine, and nefazodone had no significant impact on HRV despite patients' response to treatment.²⁴ Although tricyclic antidepressants reduce HRV, at least one study has suggested that, in patients with panic disorder, treatment with the SSRI paroxetine normalizes HRV.²⁵

Conclusion

Our patients showed some impairment of HRV indices that did not improve significantly after therapy with citalopram in future; the clinical importance of such disturbances should be evaluated in details with prolonged follow-up and greater sample size.

Limitation

- We had not a control group
 - We studied only the female patients.

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Conflict of Interests

Authors have no conflict of interests.

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