



[ORIGINAL RESEARCH]

Effects of Escitalopram on Autonomic Function in Posttraumatic Stress Disorder Among Veterans of Operations Enduring Freedom and Iraqi Freedom (OEF/OIF)

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ADDRESS CORRESPONDENCE TO:

Sriram Ramaswamy, MD, Department of Veterans Affairs Nebraska-Western Iowa Health Care System, 4101 Woolworth Avenue, Omaha, NE 68105; Phone: (402) 995-4712, Fax: (402) 995-5543, Email: Sriram.Ramaswamy@va.gov

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by **SRIRAM RAMASWAMY, MD; VITHYALAKSHMI SELVARAJ, MBBS; DAVID DRISCOLL, PhD; JAYAKRISHNA S. MADABUSHI, MD, MRCPsychiatry; SUBHASH C. BHATIA, MD; and VIKRAM YERAGANI, MBBS, DPM, FRCP(C)**

Drs. Ramaswamy, Driscoll, and Bhatia are with the Nebraska Western Iowa Veterans Affairs Healthcare System and Creighton University, Omaha, Nebraska; Dr. Selvaraj is with Creighton University, Omaha, Nebraska; Dr. Madabushi is with Baptist Health System, Birmingham, Alabama; and Dr. Yeragani is with Wayne State University School of Medicine, Detroit, Michigan, and the University of Alberta, Edmonton, Canada.

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ABSTRACT

Objective: Posttraumatic stress disorder is a chronic, debilitating condition that has become a growing concern among combat veterans. Previous research suggests that posttraumatic stress disorder disrupts normal autonomic responding and may increase the risk of cardiovascular disease and mortality. Measures of heart rate variability and QT interval variability have been used extensively to characterize sympathetic and parasympathetic influences on heart rate in a variety of psychiatric populations. The objective of this study was to better understand the effects of pharmacological treatment on autonomic reactivity in posttraumatic stress disorder.

Design: A 12-week, Phase IV, prospective, open-label trial of escitalopram in veterans with combat-related posttraumatic stress disorder and comorbid depression.

Setting: An outpatient mental health clinic at a Veterans Affairs Medical Center.

Participants: Eleven male veterans of Operations Enduring Freedom and Iraqi Freedom diagnosed with posttraumatic stress disorder and comorbid depression.

Measurements: Autonomic reactivity was measured by examining heart rate variability and QT interval variability. Treatment safety and efficacy were also evaluated pre- and post-treatment.

Results: We observed a reduction in posttraumatic stress

disorder and depression symptoms from pre- to post-treatment, and escitalopram was generally well tolerated in our sample. In addition, we observed a decrease in high frequency heart rate variability and an increase in QT variability, indicating a reduction in cardiac vagal function and heightened sympathetic activation.

Conclusion: These findings suggest that escitalopram treatment in patients with posttraumatic stress disorder and depression can trigger changes in autonomic reactivity that may adversely impact cardiovascular health.

INTRODUCTION

Posttraumatic stress disorder (PTSD) is a chronic debilitating condition resulting from exposure to life-threatening traumatic situations. The predominant symptoms of PTSD include re-experiencing of traumatic event, flashbacks, nightmares, hypervigilance, emotional numbing, and avoidant behavior. The lifetime prevalence of PTSD in the United States population is estimated to be 7.8 percent.¹ PTSD is more prevalent in veterans exposed to combat. This is especially true for Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) returnees.²

PTSD is characterized by physiologic reactivity to trauma cues and autonomic hyperarousal, which may lead to tachycardia, increased blood pressure, tachypnea, and excessive sweating. This autonomic arousal can be quantified by spectral analysis of heart rate variability (HRV). HRV is a noninvasive measure that can illuminate autonomic nervous system input on the cardiac pacemaker. HRV is the standard deviation of successive R-to-R intervals in normal sinus rhythm and reflects the interplay and balance between sympathetic and parasympathetic input on a cardiac pacemaker. Spectral power in the high frequency (HF: 0.15–0.5Hz) band reflects parasympathetic input, or cardiac vagal function. Low frequency (LF:

0.04–0.15Hz) power is related to baroreceptor control and is mediated by vagal and sympathetic systems. Several studies have reported lower resting HRV in depression and in anxiety disorders such as PTSD.^{3–7} A high degree of HRV is present in compensated hearts with good cardiac function, whereas decreased HRV is associated with severe coronary artery disease and congestive heart failure. Decreased HRV is an independent predictor of cardiac mortality in post-myocardial infarction (MI) patients. In fact, decreased HRV is shown to be a strong and independent predictor of mortality in cardiac patients as well as normal controls.⁸

In addition to HRV measurements, another parameter associated with ventricular tachycardia and sudden cardiovascular death is QT variability.^{9,10} Recent studies have shown the importance of beat-to-beat QT interval variability as a noninvasive marker of cardiac repolarization lability. An increase in QT variability is associated with severe ventricular abnormalities and sudden death.¹¹ It has been demonstrated that unmedicated patients with anxiety and depression have higher QT variability compared to normal controls.^{12,13} Whereas decreased HRV is associated with cardiac mortality, increased QT variability is associated with an increased risk of arrhythmia, presumably because there is a greater probability of the “R-on-T” phenomenon and the generation of ventricular fibrillation.¹⁰ QT variability is increased by sympathetic tone and is intriguingly reported to be greatest in the early morning hours when rates of sudden cardiovascular death are the highest.¹⁴ It has also been shown that QT variability increases significantly during the change from supine to standing position, after intravenous isoproterenol infusions and after long-term pemoline administration.^{15,16} These studies suggest that sympathetic activation

is associated with an increase in QT variability.

It has been hypothesized that the measurement of heart rate and QT variability can indicate if an illness or a treatment is increasing the risk of ventricular arrhythmias and sudden cardiovascular death.^{8,10} QT variability has not been extensively studied in PTSD. There are data demonstrating a prospective association between PTSD symptoms and coronary heart disease even after controlling for depressive symptoms.¹⁷ Thus, understanding the effects of pharmacological treatment in PTSD on HR and QT variability indices is critical.

Escitalopram is the S-enantiomer of the selective serotonin reuptake inhibitor (SSRI) citalopram, which contains equal amounts of the S- and R-forms in a racemic mixture. Escitalopram is the most selective SSRI, with almost no significant affinity to other tested receptors. Escitalopram is at least as effective in the treatment of depression and anxiety as other SSRIs, as well as venlafaxine, bupropion and duloxetine. Thus, it is an effective first-line option in the management of patients with major depression and various anxiety disorders. Escitalopram has also shown to be effective in the treatment of military veterans with PTSD.^{18,19} Escitalopram is well tolerated, has a quick onset of action, and minimal drug-drug interactions. However, it has been reported that antidepressants like citalopram and escitalopram may increase the risk of potentially fatal QT interval prolongation at higher doses.^{20–22} Currently, little is known about HRV and QT interval variability during treatment with escitalopram in patients with PTSD and/or major depression.

The primary aim of the study was to investigate the effects of escitalopram on cardiac vagal and sympathetic function in PTSD. To address this aim, we examined R-R interval variability and QT interval variability in OEF/OIF veterans

suffering from PTSD with comorbid depression. Our hypothesis was that escitalopram treatment would be associated with normalization of HRV and a decrease (or no effect, implying a lack of serious cardiac side effects) in QT variability. The secondary aim of this study was to determine the safety and efficacy of escitalopram in veterans with PTSD.

METHODS

Participants. We conducted a 12-week, prospective, open-label study in 11 male veterans with PTSD and comorbid depression recruited from the mental health clinic at the Omaha VA Medical Center. All subjects were between 19 and 55 years of age (mean [M]=28.0, standard deviation [SD]=2.6). Diagnosis of PTSD and depression was determined by the Mini International Neuropsychiatric Interview.²³ All study procedures were carried out in accordance with the Declaration of Helsinki and were reviewed by the Omaha VAMC Institutional Review Board. Informed consent of all participants was obtained after the nature of the procedures had been fully explained and prior to study participation.

Patients with a history of cardiovascular disease, hypertension, or significant medical illness were excluded from study. Patients with a lifetime diagnosis of bipolar disorder, schizophrenia, or schizoaffective disorder were excluded from this study. Patients with current suicidal or homicidal ideation were excluded from the study. Concomitant treatment with alpha adrenergic blockers, beta adrenergic blockers, ACE inhibitors, digoxin, antiarrhythmic drugs, benzodiazepines, trazodone, or medications known to have significant anticholinergic, antihistaminergic, or serotonergic properties was not permitted. Usage of zolpidem as a hypnotic was allowed. Concomitant individual and group psychotherapy were permitted. In addition, subjects could not be taking any psychotropic

medication, including SSRIs, for at least two weeks (4 weeks for fluoxetine) at the time of study entry.

Procedure. There were a total of seven study visits. We acquired 10 minutes of continuous high-resolution electrocardiogram (ECG) data in resting supine position at Visit 1 (“pre-treatment”) and Visit 7 (“post-treatment”). To assess PTSD symptoms, we used the Clinician Administered PTSD Scale (CAPS),²⁴ which is a clinician-administered scale with 17 items to assess the core PTSD symptoms listed in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*.²⁵ Higher scores on the CAPS indicate greater severity of PTSD symptoms. To assess anxiety and depression symptoms, we used the Hamilton Anxiety Scale²⁶ (HAM-A) and the Hamilton Rating Scale for Depression²⁷ (HAM-D). Higher scores on the 14-item HAM-A reflect greater severity of anxiety symptoms, while scores on the 17-item HAM-D reflect greater severity of depression symptoms. Treatment efficacy was further assessed using the Clinical Global Impression²⁸ (CGI), which is a clinician-administered scale with two items used to rate illness severity (CGI-S) and global improvement from baseline (CGI-I). Higher scores on the CGI-S reflect greater illness severity, while lower scores on the CGI-I indicate greater improvement. The CAPS, HAM-A, and HAM-D were administered at Visits 1, 4, and 7. The CGI-S was administered at all visits, while the CGI-I was measured at all visits except the first. An individually tailored and flexible-dose regimen of open-label escitalopram was utilized with 10mg/day for one week, which was increased to 20mg/day as tolerated.

A safety follow-up visit (Visit 8) was scheduled only for patients with unresolved adverse events detected prior to or at the End of Study/Early Termination visit. At the end of the study, patients were referred back to

their respective clinics for continuing treatment.

Data Acquisition. ECG signals were obtained using a Biopac Systems (Goleta, California, United States) MP150 data acquisition system and ECG100C electrocardiogram amplifier. We used 256 seconds of artifact-free data in supine position during rest and deep breathing periods.

Data reduction and analysis.

All analyses were conducted on 256-second segments of supine data sampled at 1000 Hz. QT variability was measured on a PC using Windows platform. This uses a graphical interface of digitized ECG where the time of the “R” wave is obtained using a peak detection algorithm. Then the operator provides the program with the beginning and the end of the QT wave template. This algorithm finds the QT interval for each beat using the time–stretch model. If the operator chooses a longer QT template all the QT intervals will be biased accordingly. This algorithm should only be used to study QT variability and not the mean QT. The R-R interval and QT interval data were sampled at 4Hz to obtain instantaneous HR and QT intervals. Using a 4Hz sampling rate would allow an accurate estimation of the power spectrum up to 1Hz. These data were edited using software that eliminates premature beats using a linear approach. The data were then detrended by using the best-fit line prior to the computation of spectral analyses.

The mean HR (HR_m), detrended HR variance (HR_v), mean QT interval (QT_m, detrended QT variance (QT_v), and QT_v corrected for QT_m (QT_v/QT_m squared) were calculated from the instantaneous HR and QT time series of 1024 points (256 seconds).

The principal outcome measures for QT variability in this study were QT variability normalized for mean QT interval (QT_{vm}) and the QT variability index (QT_{vi}). A normalized QT variability index was

TABLE 1. Pre- and post-treatment heart rate variability and QT measures (mean±SD)

MEASURE	PRE-TREATMENT	POST-TREATMENT	P-VALUE
RR mean (ms)	941±161	880±138	>0.05
HF (ln)			
Rest	6.31±1.16	5.48±0.67	<0.05
Deep breathing	7.37±2.57	5.74±0.82	0.06
LF (ln)			
Rest	6.53±1.11	6.05±0.86	>0.1
Deep breathing	8.37±2.77	6.62±1.14	0.05
QT mean (ms)	375±43	404±23	>0.05
QTvi			
Rest	-1.82±0.43	-1.32±0.67	<0.05
Deep breathing	-1.76±0.31	-1.66±0.40	>0.9

SD: standard deviation; HF: high-frequency power; LF: low-frequency power; ln: natural logarithm; QTvi: QT variability index.

calculated using Berger's formula:²⁹
 $QTvi = \log_{10}\{(QTv/QTm^2)/(HRv/HRm^2)\}$.
 This index represents the log-ratio between the QT interval and the RR (inter-beat interval) variance, each normalized for the corresponding mean.

HRV was indexed using both time domain measures and frequency domain measures. QT variability for RR and QT intervals were compared using time domain measures. Spectral powers of QT and R-R series were assessed using frequency domain measures of high frequency (HF: 0.15–0.5Hz) and low frequency (LF: 0.04–0.15Hz) power. A natural log (ln) transformation was applied to spectral power values to correct for skewness.

Changes over time were estimated with repeated measures, mixed-effects (ME) models. The repeated measures model included visit (as a categorical variable), as a fixed effect. Either an unstructured or autoregressive AR(1) covariance matrix was used to fit the within-subject repeated measures effect for the models. *P*-values for pairwise comparisons were adjusted with

Tukey's method, and *P*-values less than 0.05 were considered to be statistically significant. Statistical analyses were conducted using SPSS version 19.0 (IBM Corp., Armonk, New York, United States).

RESULTS

Physiological data. Data on cardiac measures are summarized in Table 1. There was no significant difference between pre- and post-treatment RR mean or QT interval mean (*P*-values for both >0.05). Analyses of the LF (ln) data at rest showed no significant change from pre- to post-treatment, $F(1,10)=2.1$, $P>0.1$. There was a marginally significant change in LF (ln) during deep breathing from pre- to post-treatment, $F(1,9)=5.4$, $P=0.05$. Further, we observed a significant decrease in HF (ln) at rest from pre- to post-treatment, $F(1,10)=7.6$, $P<0.05$. A marginally significant change was observed for HF (ln) during deep breathing from pre- to post-treatment, $F(1,9)=4.7$, $P=0.06$. Analysis of pre- and post-treatment QTvi revealed a significant increase in QTvi during rest, $F(1,10)=8.0$,

$P<0.05$. No significant change was observed for QTvi during deep breathing from pre- to post-treatment, $F(1,9)<1$, $P>0.9$.

Safety and efficacy data. During the study, there were nine nonserious adverse events reported, including five events (three cases of insomnia, one case of loose bowels, and one case of bruxism) determined to be possibly related to study drug and four events (one case of worsening asthma, one case of cough, one case of sleepwalking, and one case of irritability) determined to be unrelated to study drug. There was one reported serious adverse event (suicidal ideation) that was determined to be possibly related to study drug. In addition, there was some attrition secondary to adherence issues.

Mean scores on measures of treatment efficacy pre- and post-treatment are reported in Table 2. Scores on the CAPS, HAM-A, and HAM-D decreased significantly from Visit 1 to Visit 7 (all *P*-values <0.05). CGI-S scores at Visit 1 and Visit 7 did not differ significantly ($P=0.11$), while CGI-I scores showed a significant reduction from Visit 2 to Visit 7 ($P<0.05$).

DISCUSSION

The primary aim of the current study was to examine the effects of escitalopram treatment on cardiac vagal and sympathetic function in veterans with PTSD and comorbid depression. It was hypothesized that this treatment would result in a normalization of HRV and a decrease (or no change) in QT variability. Contrary to our hypothesis, however, we observed a significant decrease in HF HRV and increased QTvi in our sample. On the secondary outcomes measures, treatment with escitalopram was associated with improvement in PTSD and depressive symptoms. Data pertaining to drug safety further indicates that the study drug was well tolerated.

Autonomic dysregulation, including reduced HRV, has been well documented in PTSD and

depression.^{3-7,30,31} The reduction in HF HRV observed in this study suggests that treatment by escitalopram may lead to further reduction in parasympathetic (vagal) control of heart rate and reduced flexibility in autonomic responding. This finding of decreased HF HRV is consistent with previous work indicating that antidepressant use can reduce HRV and cardiac vagal control,^{32,33} which has been associated with increased risk of cardiovascular disease and mortality.

One might speculate that the observed increase in QT_{vi} is probably due to anticholinergic effect of the drug. The mean post-treatment QT interval was higher but did not reach significance in this study. This probably indicates a decrease in vagal tone and shift toward sympathetic dominance. On the other hand, the increase in QT_{vi} might also reflect a possible effect of escitalopram on the QT interval. In 2011, the United States Food and Drug Administration (FDA) released a safety announcement regarding QT interval prolongation seen at higher doses of citalopram,²⁰ with a revised warning released the following year,³⁴ and there have been other reports of QT prolongation in patients treated with citalopram or escitalopram.^{21,22,35,36} Normal QT_c values are less than 430 milliseconds (ms) in men and less than 450ms in women. For risk of sudden cardiac death, borderline QT_c in men is 431 to 450ms, and in women 451 to 470 ms. An abnormal QT_c in men is a QT_c greater than 450ms, and in women, greater than 470ms. The FDA analysis estimated that 40mg citalopram would increase QT_c interval by 12.6ms. As drug-induced QT prolongation is more likely to be clinically significant in patients with cardiac risk factors,³⁷ clinicians should be aware of such risk factors when prescribing these medications and provide additional monitoring as needed, particularly for patients who are using other QT-prolonging agents. Such measures include avoiding use of escitalopram or citalopram in patients with long QT

TABLE 2. Pre- and post-treatment scores on measures of treatment efficacy (mean±SD)

RATING SCALES	PRE-TREATMENT	POST-TREATMENT	P-VALUE
CAPS (total)	74.4±19.6	36.7±22.6	<0.001
HAM-A (total)	19.2±10.0	6.3±4.0	0.001
HAM-D (total)	15.6±6.3	4.3±4.6	<0.001
CGI-S	4.6±0.8	3.6±1.3	0.111
CGI-I	3.0±1.1	1.9±0.6	0.026

Note: As the CGI-I is not obtained at baseline (Visit 1), Visit 2 scores are reported for Pre-treatment.

SD: standard deviation; CAPS: Clinician Administered PTSD Scale; HAM-A: Hamilton Anxiety Scale; HAM-D: Hamilton Rating Scale for Depression; CGI-S: Clinical Global Impression-Severity; CGI-I: Clinical Global Impression-Improvement.

interval and monitoring and correcting hypokalemia and hypomagnesaemia.

Limitations. There are a number of limitations that should be acknowledged in this study. First, due to the small sample size, further research is needed to validate these findings. Second, as there was no placebo or control group for comparison in this study, we cannot rule out the possibility that factors other than escitalopram treatment contributed to our findings. Also, we did not obtain QT corrected (QT_c) from the initial 12-lead ECG recording according to Bazett's formula.³⁸ Instead, our study was designed to calculate QT_{vi}. The procedure of calculating QT_{vi} utilized in our study is not an accurate way to calculate QT_c as it is set by the person choosing a lead that has a good "R" wave. QT_c (a measure of the time between the start of the Q wave and the end of the T wave adjusted for heart rate) is usually digitally calculated by EKG machines. However, none of the commercially available software guarantees reliable estimates of this interval due to technical difficulties in identifying the end of the T-wave before it merges with the baseline. We calculated QT_{vi} by Berger's formula which, like QT_c,

is a measure of cardiac repolarization lability and marker of sudden death and malignant ventricular arrhythmias. Ours is the first study to report QT_{vi} changes following escitalopram therapy in PTSD.

CONCLUSION

In conclusion, we found that escitalopram treatment was associated with a significant reduction in clinical symptoms in veterans with PTSD and comorbid depression, though we also observed decreased HRV and increased QT variability in our sample. Increased QT variability and decreased HRV have each been associated with a greater risk of cardiovascular disease and mortality, and it is conceivable that the two in combination may increase this risk even further. Given the increased risk of mortality in patients with depression and anxiety, it will be important for future research to further address the long-term health implications of antidepressant treatment for PTSD and depression.

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