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The effect of venlafaxine on ECG intervals during treatment for depression in older adults

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Abstract

Purpose/ Background: Venlafaxine is a commonly used antidepressant with both serotonergic and noradrenergic activity. There are concerns it may prolong the corrected QT interval (QTc), and older adults may be at higher risk for this adverse effect, especially at higher dosages of the medication.

Methods/Procedures: In this secondary analysis of a prospective clinical trial, we measured changes in QTc and other ECG parameters in 169 adults aged ≥60 with a major depressive disorder treated acutely with venlafaxine extended release (XR) up to 300 mg daily. We examined the relationship of venlafaxine dosage and ECG parameters, as well as the relationship between serum levels of venlafaxine and ECG parameters.

Findings/Results: Venlafaxine exposure was not associated with an increase in QTc. Heart rate increased with venlafaxine treatment, while the PR interval shortened, and QRS width did not change significantly. QTc change from baseline was not associated with venlafaxine dosages or

serum concentrations. Age, sex, cardiovascular comorbidities, and depression remission status did not predict changes in QTc with venlafaxine.

Implications/Conclusions: Venlafaxine treatment did not prolong QTc or other ECG parameters, even in high dosages in older depressed adults. These findings indicate that venlafaxine does not significantly affect cardiac conduction in most older patients.

Keywords

Venlafaxine; QTc; ECG; Serum levels; Late life depression

Introduction

Venlafaxine is a serotonin-norepinephrine reuptake inhibitor (SNRI) recommended for¹ treating late-life depression because of its effectiveness², low cost, ease of use with once-daily dosing in the extended release (XR) form, and minimal drug-drug interactions³. The effectiveness of venlafaxine has been attributed partly to noradrenergic reuptake inhibition⁴, particularly at dosages higher than 150 mg/day^{4,5}. Venlafaxine's noradrenergic activity, however, has led to concerns regarding potential cardiovascular adverse effects, such as causing hypertension and orthostatic hypotension^{6,7}. Adverse effects of antidepressants such as venlafaxine may be especially troubling for older adults who have age-related physiological changes, multiple comorbid medical conditions, and a high risk of complications from polypharmacy⁸.

Concerns have been raised regarding the effect of SNRIs and selective serotonin reuptake inhibitors (SSRIs) on electrocardiogram (ECG) changes, particularly the corrected QT interval (QTc). Several antidepressants have been postulated to prolong the QTc, which is a risk factor for sudden cardiac death⁹ by increasing the risk for Torsades de Pointes (TdP), an arrhythmia that can lead to ventricular fibrillation and cardiac arrest. Increased QTc interval has become a proxy marker for drug-induced risk of sudden cardiac death¹⁰ and several studies have demonstrated that some specific antidepressants prolong the QTc^{11,12}. While some studies have cause concern regarding SSRIs such as citalopram and QTc prolongation¹³, there is question regarding the true risk for resulting ventricular arrhythmias or death¹⁴. The risk of QTc prolongation and its clinical significance from therapeutic doses of different antidepressants remains a controversial topic.

Preclinical evaluations of venlafaxine have not indicated that venlafaxine likely causes drug-induced QTc prolongation. Blockade of the hERG channel, a potassium channel that when mutated causes long QT syndrome and arrhythmias¹⁵, is now used in drug development as an indicator for potential QTc-prolonging risk. Venlafaxine is not a potent inhibitor of hERG, and only demonstrates blockade at levels significantly higher than in therapeutic range, with an IC₅₀ of 28 μM (effective concentration of 659 nM)¹⁶. While the hERG IC₅₀ of desvenlafaxine has not been published to our knowledge, the product monograph for Pristiq, desvenlafaxine's brand name, indicates that desvenlafaxine did not inhibit hERG up to desvenlafaxine concentrations of 195 μM.

Clinical evaluations of venlafaxine, however, have been less conclusive. Some case reports and studies have suggested that venlafaxine may prolong the QTc^{6,17–19}, while others have not found this effect^{20–25}. Variations in venlafaxine metabolism due to age, genetic variants in CYP2D6^{26,27}, and co-prescribed medications may contribute to these discrepant findings. For example, genetic variations leading to high serum venlafaxine and O-desmethylvenlafaxine concentrations have been postulated to contribute to possible cardiac toxicity in overdose²⁸. A study from post-mortem samples suggested that peripheral serum concentrations of venlafaxine correlate with cardiac serum or tissue concentrations of venlafaxine and O-desmethylvenlafaxine²⁹. Therefore, it is important to examine not only the dosage but also the serum concentration of venlafaxine and O-desmethylvenlafaxine when assessing its effect on ECG.

While studies of the impact of antidepressants on ECG changes typically focus on the QTc due to its association with sudden cardiac death, other clinically-meaningful ECG parameters can also be altered by antidepressants, such as PR interval prolongation and QRS widening with tricyclic antidepressants³⁰. Therefore, we performed a secondary analysis from a previously published clinical trial³¹ to examine the relationship between measured venlafaxine and O-desmethylvenlafaxine serum concentration and pre- and post-treatment ECGs in older adults with a major depressive disorder (MDD) treated with venlafaxine 150–300 mg/day over the course of up to 14 weeks. We hypothesized that if venlafaxine is associated with changes in the QTc, QRS, or PR intervals, these changes would correlate with both dosages and serum concentrations.

Materials and Methods

Data analyzed in this study was obtained during the open-label phase of the multicenter (Pittsburgh, St. Louis, and Toronto) clinical trial “Incomplete Response in Late Life Depression: Getting to Remission” (IRL-GRey). The protocol for this NIMH-funded clinical trial has been described previously ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00892047) identifier: [NCT00892047](https://clinicaltrials.gov/ct2/show/study/NCT00892047))³¹. Briefly, participants were aged 60 years or older, had a diagnosis of a current major depressive episode via the Structured Clinical Interview for Axis I DSM-IV Disorders³², and had a Montgomery-Asberg Depression Scale (MADRS)³³ score ≥ 15 . We included only participants who had both baseline and follow-up ECGs and those with evidence of venlafaxine intake as determined by serum measurements. We excluded those already using venlafaxine at the start of study. Open treatment with venlafaxine XR was started in participants following a protocolized titration schedule. The initial dosage was 37.5 mg/day, titrated over 2 weeks to a target dosage of 150 mg/day in increments of 37.5–75 mg during intervals of at least 3 days. After 6 weeks, venlafaxine XR was further titrated to a maximum of 300 mg/day in participants who did not demonstrate remission of their depressive symptoms (defined as a MADRS score ≥ 10). Overall, participants received 12–14 weeks of venlafaxine open-label treatment.

Measures

Clinical characteristics including medical comorbidities were assessed at a baseline visit via medical record diagnoses and quantified with the Cumulative Illness Rating Scale for

Geriatrics (CIRS-G)³⁴. Serious adverse events were recorded, including death and any admissions to a hospital.

ECGs were obtained at a pretreatment visit and at the final visit of the open-label treatment phase. The St Louis and Pittsburgh sites used the MAC 5500 HD (General Electric, Chicago, IL) ECG equipment, which calculates the QTc using Bazett's formula, $QTcB = QT / \sqrt{RR}$. At the Toronto site, ECGs were obtained with either a Philips Pagewriter Touch Cardiograph (Philips, Amsterdam, Netherlands), which uses the same QTcB formula, or a Hewlett Packard Pagewriter Xli (Hewlett Packard, Palo Alto, CA), which uses Fridericia's formula; $QTcF = QT / (RR)^{1/3}$. For this analysis, we recalculated all the QTc intervals using Fridericia's formula based on the QT and RR output. We considered a QTc to be "prolonged" if it was ≥ 450 ms for males and ≥ 460 ms for females³⁵.

ECG parameters as generated by the ECG machines were entered into a database throughout the study. Due to the secondary nature of our analysis, the ECGs themselves were not available for review. Therefore, qualitative descriptions such as abnormal rhythms or bundle branch blocks were not available for all ECGs and were not included in analyses or exclusion criteria. Included participants were, however, required to have both pre- and post-treatment ECGs in order to account for baseline differences in ECG characteristics that could impact ECG interval calculations, allowing for isolation of venlafaxine-specific effects.

A blood sample was collected at the final visit. Due to logistical reasons and the secondary nature of this analysis, the samples were not required to be drawn at a specific dosage interval, but were obtained at the same visit as the ECG for the majority of participants. Serum specimens were obtained and kept at -80°C until the serum venlafaxine and O-desmethylvenlafaxine concentrations were determined. Standards were from Cerilliant (Round Rock, TX), and reagents (acids, bases, solvents) were Fluka brand (Honeywell, Morristown, NJ). Venlafaxine and its active metabolite O-desmethylvenlafaxine were quantified by LC-MS/MS after solvent extraction at alkaline pH; 100 μL of sample or standard was combined with 50 μL of deuterated internal standard mix (venlafaxine-D6, 100 ng/mL in 30% methanol) and 50 μL of 1N ammonium hydroxide (pH 9.5–10), then extracted with 3 mL of ethyl acetate. Extract was acidified with 50 μL of HCl-methanol, dried under nitrogen and reconstituted in 200 μL of mobile phase (55 % of 10 mM ammonium acetate pH 5, 10 % of 0.1 % formic acid, and 35 % acetonitrile). A 20 μL injection was made onto a Kromasil C18 column (50 mm $\times$ 4.6 mm, 3.5 μm) on an Acquity UPLC system (Waters, Milford, MA) connected to a TSQ Quantum Ultra (AM) triple quadrupole mass spectrometer (ThermoFisher Scientific, Waltham, MA). Analytes were separated in a 5.5 min, isocratic run with a flow rate of 300 $\mu\text{L}/\text{min}$. Retention times were 2.1 min for venlafaxine and 1.7 min for O-desmethylvenlafaxine. Venlafaxine concentrations were assessed against a calibration curve linear from 1 to 1000 ng/mL with a 1/x weighting (assay CV < 10%). The following transitions were monitored in positive ESI mode: Venlafaxine: 278 $\rightarrow$ 121, Venlafaxine-D6: 284 $\rightarrow$ 121, O-desmethylvenlafaxine: 264 $\rightarrow$ 107. Because venlafaxine and O-desmethylvenlafaxine are both psychoactive compounds, the sum of the two concentrations was used in the analysis as the total active moiety.

The blood sample and the ECGs were typically obtained during the same visit. For logistical reasons, this was not possible for a minority of participants. In these cases, the ECG and blood sample were taken at similar times of the day. The blood samples were not required to be taken at venlafaxine trough time (i.e. immediately before the daily dose) because the serum levels were not being used as therapeutic drug monitoring. Therefore, the venlafaxine total active moiety serum levels were not compared with the reference ranges that have been suggested for potential venlafaxine therapeutic drug monitoring (e.g. 195–400 ng/ml). Similarly, serum levels were therefore not compared to dosages, but only to ECG changes.

Statistical Analysis

Analyses were performed using SAS 9.4. (SAS Institute Inc., Cary, North Carolina) and Tableau 2019.3 (Tableau Software, Seattle, WA). All reported p-values are 2-tailed, with significance level for all tests set a priori at $p = 0.05$. ECG parameters included the heart rate, QTc, QT, QRS, and PR intervals, collected pre- and post- treatment. In a first set of analyses, we assessed the relationship between the change in QTc and the venlafaxine dosages. We also separately assessed the relationship between QTc change and serum venlafaxine, serum O-desmethylvenlafaxine, and serum venlafaxine plus O-desmethylvenlafaxine concentrations. We repeated these analyses for the heart rate and the other ECG parameters. For these analyses, paired t-tests were used to compare the QTc, heart rate, and other ECG parameters pre- and post- treatment with venlafaxine XR. The association between changes in these measures and venlafaxine XR dosages or serum concentrations was assessed with Pearson correlation coefficients. Linear regression models were applied to estimate the strength of these associations before and after controlling for relevant covariates (age, sex, and history of cardiac disease as measured with the CIRS-G score of the cardiac system).

We also examined the mean change in QTc from pre-post treatment with venlafaxine in those whose depression did remit with treatment (i.e., with a MADRS score of 10 or less post-treatment), compared to those whose depression did not remit. This comparison was conducted because depression has been demonstrated to be related to cardiovascular health³⁶. We used a restricted maximum likelihood-based mixed model for repeated measures (MMRM) including timepoints, subgroups, and group-by-timepoint interaction. When the group-by-timepoint interaction was significant, contrasts were used to compare the mean change over time between two subgroups based on the least squares (LS) means for the subgroup's group-by-timepoint interaction in the MMRM-model.

Results

Of the 468 participants who started open-label venlafaxine XR, 274 (59%) did not have complete ECG data at baseline and when completing 12–14 weeks of venlafaxine XR treatment: 91 due to participant withdrawal or administrative reasons for not completing this phase of the study, 147 because they responded to venlafaxine XR and did not complete the final ECG due to the logistics of the study, and 35 were non-responders but did not have both pre- and post-treatment ECG. There was also one death by suicide leading to incomplete ECG data. Of the remaining 194 participants with complete ECG data, 25

participants were excluded for either being on venlafaxine at baseline or having a venlafaxine serum concentration of zero (suggesting complete lack of adherence). The remaining 169 participants were included in this analysis and their demographic and clinical characteristics are described in Table 1.

ECG Parameters

QTc significantly shortened by a mean (SD) of 3.7 ms (± 16.7 ; 95% CI: 1.2–6.3) from pre- to post-treatment (Table 2). Using our QTc cutoffs of 450 ms for males and 460 ms for females, there were 13 participants (7.7%) with a prolonged QTc pre-treatment and 8 (4.7%) post-treatment. The QT interval also significantly shortened by a mean of 11.1 ms (± 25.9 ; 95% CI: 7.2–15.0) while the heart rate significantly increased by a mean of 3.6 beats per minute (± 9.7 ; 95% CI: 2.1–5.0). The PR interval also significantly shortened by a mean of 3.4 ms (± 11.1 ; 95% CI: 1.7–5.1). The QRS width did not change significantly. Changes in QTc were not associated with venlafaxine dosages ($r = -0.12$, $p = 0.13$) (Figure 1). Pre and post treatment QTc values for males and females are demonstrated in Supplemental Figure S1.

QTc change was not linearly correlated with serum concentration of venlafaxine plus O-desmethylvenlafaxine (Figure 2). QTc change was also not linearly correlated with serum venlafaxine or serum O-desmethylvenlafaxine concentrations examined separately (data not shown). While total active moiety concentrations demonstrated statistically significant correlations with increasing heart rate ($r^2 = 0.05$, $p = 0.003$) and decreasing QT interval ($r^2 = 0.04$, $p = 0.009$), the associated R-squared values are extremely small, suggesting these correlations are not clinically significant. There was no linear association between any serum concentrations and changes in QRS or PR intervals. The regression analysis (including age, sex, and history of cardiac disease) did not show an independent association between QTc and total active moiety serum concentration ($F = -0.60$, $df = 1$, $p = 0.44$), and none of the potential confounders were significant mediators.

The subgroup analysis examined whether depression remission status impacted venlafaxine's effect on QTc by comparing remitters and non-remitters. There was no impact of depression remission status on QTc prolongation, as there was no statistical difference ($p = 0.47$) in QTc pre to post-treatment change between depression remitters (-2.1 ms, $SE = 2.61$, $p = 0.0045$) and non-remitters (-4.26 ms, $SE = 1.48$, $p = 0.42$).

Potential Cardiac-Related Adverse Events

There was one completed suicide during the open-label phase of the study. There were no sudden cardiac deaths, other deaths, or known occurrences of Torsades de Pointes. One participant had an arrhythmia following a syncopal event while on venlafaxine XR. Evaluation revealed PVCs and recurrent supraventricular tachycardia. Electrophysiology study revealed the existence of an atrio-ventricular accessory pathway, which was successfully ablated. Beta blocker medication changes closely preceding the event was also thought to be a contributing factor. The participant's QTc on admission was 484 (baseline measured 442), and venlafaxine was tapered and discontinued as a precautionary measure by the cardiology team. There were no ventricular arrhythmias.

Discussion

To our knowledge, this is the first study that prospectively evaluated the relationship between venlafaxine dosage and serum concentrations with ECG changes in a geriatric population. We had three main findings. First, the mean QTc did not increase and actually shortened slightly after 12–14 weeks of treatment with venlafaxine XR. Second, venlafaxine and total active moiety serum concentrations did not correlate with QTc changes. Third, there was no effect of sex, cardiac disease, or depression remission status on these results. These findings suggest that venlafaxine can be used in a group of older depressed patients at relatively high risk for QTc prolongation because of age, depression status, and co-morbid cardiovascular disease.

In our study, even high dosage of venlafaxine XR (i.e., 300 mg/day) did not prolong the QTc. Severity of cardiac comorbidities (based on CIRS-G scores of the cardiac system) did not predict the effect of venlafaxine on the QTc. This negative finding is consistent with some previous studies of older patients with stable medical conditions taking venlafaxine^{21,25}. In a previous small study, two cases of prolonged QTc were reported (defined as ≥ 440 ms in this study) among 40 older depressed patients, for an incidence of 5% (2/40)⁶: QTc increased from 403 ms to 456 ms in one patient and from 433 ms to 469 ms in another one. Different criteria can be used to define a clinically meaningful QTc prolongation; in the current study we used a QTc ≥ 450 for males, ≥ 460 for females³⁵. However, more lenient criterion requiring an increase from baseline by 60 ms and QTc > 480 ms has also been used in studies examining QTc prolongation in antidepressants³⁷. Neither of these two patients from the earlier study would have met these more lenient criteria for QTc prolongation. Additionally, in this earlier study Bazett's formula was used to calculate QTc, and this equation is known to overcorrect at higher heart rates³⁵.

An important aspect of the current study is the measurement of venlafaxine and O-desmethylvenlafaxine serum concentrations to account for differences in venlafaxine adherence and metabolism. Polymorphisms in CYP2D6, the major metabolizer of venlafaxine to O-desmethylvenlafaxine³⁸ have been shown to impact serum venlafaxine concentrations in a geriatric population²⁷. A theoretical concern with venlafaxine is that poor metabolizers might have high enough venlafaxine concentrations to cause QTc prolongation. Thus, even if there is no overall increase in QTc, a few patients may still be at risk because the same dosage can yield various concentrations. Our study does not support this concern: despite a 10-fold variation in its range, serum venlafaxine concentration was not correlated with QTc changes (see Figure 2A). Participants with higher serum concentrations of venlafaxine, O-desmethylvenlafaxine, or total active moiety concentrations did not have an increase in QTc interval from baseline.

In a recent study, Hefner et al reported a positive correlation between serum venlafaxine concentrations and QTc in 34 older patients¹⁸. There were two methodologic differences that may account for our different results. First, our study was prospective, allowing us to account for baseline QTc. Second, it is possible these different results are due the use of Fridericia's formula, whereas Hefner et al did not report the QTc formula they used. The specific QTc formula is important in determining true cardiac risk, particularly within drugs

that increase the heart rate. Venlafaxine has been shown to increase the heart rate in a small but statistically significant manner^{24,39,40}, as it did in our study. Thus, using the appropriate QTc formula is particularly important with venlafaxine to avoid over-correcting the QT interval. The most commonly used formula (Bazett's, $QTcB = QT / \sqrt{RR}$) is known to overcorrect at high and low heart rates, causing inappropriately elevated QTc interval values and Fridericia's formula ($QTcF = QT / (RR)^{1/3}$) is superior in this regard⁴¹. Other studies have demonstrated that evaluation of drug-induced QTc changes is affected by the choice of QTc formula⁴². These methodologic differences may also account for some previous reports that venlafaxine prolongs the QTc both at therapeutic doses¹⁷ and in overdose¹⁹. However, the effect in overdose has been recently questioned, underscoring the importance of which QTc formula is used⁴³. Typically, prospective studies have not observed an effect of venlafaxine on the QTc interval^{21–25}.

There are important limitations to our study. First, the study did not have a placebo group, limiting our ability to control for clinical variables that may confound the relationship between QTc, venlafaxine dosage, and serum concentrations. Although we accounted for baseline QTc interval and some potential confounders in the regression model, there could be additional confounders that were not investigated. Second, there was no positive control in the study design (e.g. participants prescribed a known QTc-prolonging compound, such as moxifloxacin), so we are unable to conclude with certainty that this study would detect drug-induced QTc prolongation. Third, there was a large number of participants excluded for our analysis, including participants who discontinued participation in the clinical trial (19%) and those that continued with the trial but did not have both pre-treatment and post-treatment ECGs (39%). This significant exclusion percentage could have impacted our ability to accurately detect QTc changes in a more generalizable population. The majority of participants who continued in the trial but were missing a follow-up ECG were in remission from depression at the end of venlafaxine trial, which could have introduced a confound for those who were not included in our analysis.

A fourth limitation is that complete ECG descriptions were unavailable in two-thirds of participants due to the secondary nature of our analysis. Thus, we were unable to account for rhythms such as atrial fibrillation or bundle branch blocks, which can impact the accuracy of QTc calculations. However, some studies suggest that the QTc Fridericia formula we used is an appropriate formula for determining QTc in atrial fibrillation^{44,45}. Finally, the generalizability of the results is limited to older individuals in their 60's and 70's whose medical comorbidities were stable enough to have participated in and completed our clinical trial. The results cannot be directly applied to very old patients (i.e., those in their 80's or 90's) or those with comorbidities such as unstable (e.g., ischemic) cardiac disease. However, the inclusion of patients with a history of cardiac disease allows for a greater level of generalizability than many previous studies.

While our study was not powered to detect rare events (e.g., with an incidence of less than 1%), it is still important to note that there were no cases of Torsades de Pointes or sudden cardiac death with venlafaxine dosages up to 300 mg/day and serum active moiety concentrations up to 1800 ng/ml in a relatively high-risk population. This has important implications for clinical practice, as our findings suggest that venlafaxine could be initiated

in older adults without ECG monitoring. In an era when telehealth is becoming increasingly utilized, and often necessary, these results suggest that venlafaxine could be initiated remotely without the need for an in-person baseline or follow-up ECG. Overall, our results suggest that therapeutic doses of venlafaxine do not prolong the QTc in older patients with late-life depression, or if it does, it is very rare.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Conflicts of Interest and Source of Funding:

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Figure 1.
Change in QTc from pre- to post-treatment as a function of final venlafaxine dosage – Low: 150 mg/day; moderate: 187–263 mg/day; high: 300 mg/day.

Figure 2.

Serum total active moiety concentration (venlafaxine + O-desmethylvenlafaxine) and changes in ECG parameters. **A.** QTc interval. **B.** QT interval. **C.** QRS interval. **D.** Heart rate. **E.** PR interval.

Table 1.

Demographic and clinical characteristics of the 169 participants.

	Frequency (%)		Mean ($\pm$ SD, range)
Female	104 (61.5%)	Age	67.9 ($\pm$ 6.5, 60–91)
Race		BMI	30.2 ($\pm$ 6.7, 17.3–57.4)
White	150 (88.8%)	Cumulative Illness Rating Scale for Geriatrics[*] - Count	5.9 ($\pm$ 2, 1–11)
Black	15 (8.9%)	Cumulative Illness Rating Scale for Geriatrics[*] - Total Score	9.4 ($\pm$ 4, 1–21)
Asian	3 (1.8%)	Cumulative Illness Rating Scale for Geriatrics[*] - Cardiac System Score	0.66 ($\pm$ 1.1, 0–3)
Native American	1 (0.6%)	Baseline Montgomery-Asberg Depression Scale^{**}	27.9 ($\pm$ 5.7, 15–43)
Comorbid pre-existing diagnoses		Final Montgomery-Asberg Depression Scale^{**}	18.9 ($\pm$ 9.8, 0–39)
Heart disease	28 (16.6%)	Venlafaxine serum concentration	225 ($\pm$ 228, 8 – 1546)
Arrhythmia	14 (8.3%)	O-desmethylvenlafaxine serum concentration	344 ($\pm$ 150, 16 – 741)
Hypertension	88 (53.3%)	Total active moiety serum concentration^{***}	569 ($\pm$ 268, 62 – 1820)
Diabetes	21 (12.7%)		
Use of concomitant QTc-prolonging medication[†]	69 (40.8%)		

^{*} Cumulative Illness Rating Scale for Geriatrics includes 14 organ systems rated on 0–4 for severity, count = number of organ systems (out of 14), total score = sum of severity scores of 14 systems (with score of 0 to 4 for each system and a total of 0–56).

^{**} Montgomery-Asberg Depression Scale, depression score out of 60 with higher scores indicating more severe depression (e.g., 18 moderate depression, 35 severe depression).

^{***} Sum of venlafaxine and O-desmethylvenlafaxine serum concentration.

[†] Participants that used a QTc-prolonging medication throughout the entire trial (at pre and post-treatment ECGs).

Table 2.

ECG parameters before (pre) and after (post) treatment with venlafaxine XR.

ECG parameter	Pre-Treatment				Post-treatment				Change from pre- to post-treatment			
	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	t-value	p-value
QTc	416.5	25.4	361.9	493.2	412.8	23.8	346.0	486.9	– 3.74	16.69	–2.91	0.0041
QT	400.9	39.3	308	496	389.8	33.1	309	474	– 11.11	25.88	–5.58	<0.0001
QRS width	90.7	18.5	65	180	90.8	20.1	60	192	0.16	6.71	0.31	0.7573
PR	167.5	23.6	110	258	164.1	24.2	110	278	– 3.39	11.07	–3.98	0.0001
Heart rate	69.1	13.0	45	107	72.6	11.8	48	106	3.55	9.74	4.74	<0.0001