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QTc Interval Screening in an Opioid Treatment Program

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Abstract

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Presentations

This study was presented orally at the American Society of Addiction Medicine, National Meeting Atlanta, GA, April 21, 2012 and subsequently as a poster presentation at the American Association for the Treatment of Opioid Dependency, Las Vegas NV, April 27, 2012.

Ethical Principals

The material has not been published in whole or in part elsewhere and the paper is not currently being considered for publication elsewhere; all authors have been personally and actively involved in substantive work leading to the report, and will hold themselves jointly and individually responsible for its content; all relevant ethical safeguards have been met in relation to patient or subject protection, or animal experimentation, including, in the case of all clinical and experimental studies review by an appropriate ethical review committee and written informed patient consent. The research complies with the World Medical Association Declaration of Helsinki.

Declaration of Interests

Data management and statistical analysis was supported by the Colorado Clinical Translation Science Institutes. Qualitative evaluation and analysis was supported by the Glassman Endowment. Dr. Krantz was partially supported by AHRQ Grant 1 P01 HS021138-01. Dr. Krantz was a member of the FDA Cardiovascular and Renal Drugs Advisory Committee and attended the joint meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee on July 22 and 23, 2010 that including discussion of methadone and arrhythmia risk. He has served as a consultant for design of a thorough QTc interval study for Reckitt Benckiser Pharmaceuticals Inc. (no personal remuneration) and CoLucid Inc (minimal). The RADARS® System is a division of Denver Health and Hospital Authority, a state governmental organization. The RADARS® System provides post-marketing surveillance of prescription medications to pharmaceutical manufacturers. Several manufacturers of controlled substances are subscribers to the RADARS® System. Jun Sun, Vaishali Khatri and Becki Bucker-Bartelson are employees of Denver Health and Hospital Authority, which operates the RADARS® System. They have no direct financial or non-financial relationships with pharmaceutical companies outside of their roles at Denver Health and Hospital Authority. No other authors report relevant disclosures of financial or other interest.

Methadone is highly effective for opioid dependency, but it is associated with torsade de pointes. Although electrocardiography (ECG) has been proposed, its utility is uncertain since an ECG-based intervention has not been described. An ECG-based cardiac safety program among methadone-maintenance patients was evaluated in a single opioid treatment program from 9/1/2009 to 8/31/2011 in the United States. Time from pre-treatment to repeat ECG among new entrants was assessed. The proportion with marked QTc-prolongation (> 500 ms) and the effect of the intervention on the QTc-interval in this group were evaluated. Multivariate predictors of QTc-interval change were assessed using a mixed effects model. Among 531 new entrants, 436 (82%) received at least one ECG tracing and 186 (35%) had pretreatment ECG performed. Median time to follow-up ECG was 43 days but decreased over time ($p<0.0001$). In 21 individuals with a QTc-interval > 500 ms, mean QTc-interval from peak to final ECG decreased significantly [−55.5 ms, 95% CI (−77.0 to −33.9 ms), $p=0.001$] and 12 of 21 (57.1%) dropped below the 500 ms threshold. Among new entrants with serial ECG, only methadone dose ($p=0.009$) and pretreatment QTc-interval ($p<0.0001$) were associated with the magnitude of QTc-interval change. This suggests that implementation of an ECG-based intervention in methadone maintenance can decrease the QTc-interval in high-risk patients; clinical characteristics alone were inadequate to identify patients in need of ECG screening.

Keywords

QT prolongation; ECG; Torsade de Pointes; Methadone; Arrhythmia

INTRODUCTION

Methadone is a long acting μ-opioid agonist that is highly effective for the treatment of opioid dependency.[1] Among the opioid drug class, methadone is prescribed to a minority of patients, but is disproportionately implicated in opioid-related deaths.[2] While the higher lethality of methadone likely reflects its potency and long half-life,[3] it is known to block the cardiac delayed-rectifier potassium ion-current (Ik_r)[4] and has been associated with prolongation of the rate corrected QT interval (QTc) and torsade de pointes.[5] On a morphine-equivalent basis, the mortality rate for methadone is higher than all other prescription opioids,[6] which might in part reflect methadone's proarrhythmic properties. Recent data from the US Food and Drug Administration (FDA) from 2004–2011 suggest that methadone is currently the most frequently reported drug associated with QTc prolongation and torsade de pointes.[7]

The US Substance Abuse and Mental Health Services Administration's (SAMHSA) Center for Substance Abuse Treatment convened a cardiac expert panel, which in 2009 published a guideline recommending electrocardiography (ECG) for QTc interval assessment in opioid treatment programs (OTPs).[8] However, controversy regarding the potential of ECG to increase costs, create barriers to care, and uncertainty about feasibility has limited its adoption.[9–13] In response to qualitative field review, SAMHSA reconstituted the expert panel and revised the guideline.[14] Both the revised SAMHSA guidance[14] and the American Association for Treatment of Opioid Dependency QTc interval Screening Policy and Guidance Statement[15] suggest ECG only for patients with multiple clinical risk factors for

arrhythmia, despite a paucity of evidence for a risk factor-based approach. The SAMHSA panel noted concerns regarding the potential of an ECG-based intervention to restrict access to limited therapeutic options, potential challenges due to insufficient support staff, and uncertainty regarding the appropriateness of computerized (automated) QTc interval measurements. Most importantly, a real-world demonstration of an outpatient intervention to mitigate risk has not been described for methadone or other QTc-prolonging drugs. Given this background, we assessed the feasibility and impact of implementing a pilot ECG-based cardiac safety program using computer-generated QTc measurements among methadone maintenance patients.

METHODS

The study was approved by the local Institutional Review Board (Protocol #11-1168) to evaluate the impact of a cardiac safety program. The program was initiated in an outpatient OTP that provides opioid substitution for a predominantly indigent population affiliated with an urban public hospital. Other than purchase of a single ECG machine ($4600), no additional staff hires or institutional resources were provided to support the program. The implementation team consisted of an addiction psychiatrist, an addiction fellow, and internal medicine physician. Support staff included the program director, behavioral health technicians, and registered nurses. Nurses and technicians were trained in ECG acquisition by the hospital cardiology division. No regular cardiology oversight was provided. Methadone was dispensed under direct nursing supervision and dose tracking performed using Creative Socio-Medics M4 Patient Workbench (Net Smart Technologies, Long Island, NY). All doses were titrated to achieve abstinence from illicit opioids. Preliminary implementation commenced 9/1/2009.

The following recommendations from published Cardiac Safety guidelines for methadone[11,17] were considered: 1) Disclose arrhythmia risk; 2) Assess for a history of heart disease, arrhythmia, and syncope; 3) Obtain pretreatment ECG among new entrants and perform a follow-up within 30-days; 4) If the QTc-interval exceeds 500 ms, consider discontinuation or reduction of the methadone dose; elimination of contributing factors, and 5) Consider interactions between methadone and other QTc-prolonging drugs. 6) Provide patient educational materials that explain cardiac risk; and 7) Educate OTP clinical staff about QTc-prolongation. Formal patient and provider education was not instituted. The decision to perform additional ECG among patients with doses exceeding 100 (or 120) mg/day occurred at the discretion of treating physicians. The program was integrated into routine care, and all ECGs were performed on-site prior to dosing. No algorithms specifying clinical actions or methadone dose-adjustments were utilized by physicians. Patients were verbally informed of the rationale for ECG to ensure safety. The behavioral health technician scheduled both pretreatment and follow-up ECG in coordination with the dosing nurse.

Trough-concentration ECG measurements were acquired with a Pagewriter Trim III ECG machine (Philips, Netherlands) and a computer-generated QTc-interval calculated by superimposed median complexes. In order to assess differences between computer-generated QTc-interval and manual readings among patients in whom the cardiac safety

program was applicable, a single electrophysiologist manually reviewed all tracings with any computer-generated QTc ≥ 450 ms. Measurements were performed retrospectively using on-screen digital calipers (Philips, Xcelera, Netherlands). Tracings were reclassified if the manual and computer-generated QTc intervals differed by > 10 ms or if the automated heart rate calculation was spurious due to high-frequency artifact. The QTc interval was defined as the time between the initial deflection from the isoelectric PR interval to the return of the T-wave derived from the longest measurement in any lead. The QTc was calculated using Bazett's formula for both automated and manually-derived values since this formula was recommended[8,14] as the standard rate-correction method in clinical practice.

Data were collected using a secure web-based application (Research Electronic Data Capture, REDCap, Version 4.8.2).[16] Pertinent medical history and clinical data were abstracted for patients with an initial QTc interval exceeding 450 ms by a single abstractor. Categorical variables were summarized as frequency distributions; continuous variables as mean, median, standard deviation, and interquartile range. All tests were two-sided, and a $p < 0.05$ was considered statistically significant. Statistical analyses were performed using SAS version 9.3 (Cary, NC).

Baseline clinical characteristics were analyzed among 3 pre-specified groups including the complete cohort of new entrants, those with a QTc interval 450–499 ms, and patients with marked QTc-prolongation (at least one value exceeding 500 ms). Concomitant medications were categorized by therapeutic class, and grouped as QTc-prolonging or not. The QTc interval 450–499 ms and marked QTc-prolongation groups were compared. A Student's t-test was used for comparing mean age and Fishers exact test was applied for categorical variables. For analysis of median time to repeat ECG, patients were grouped into four sequential 6-month periods based upon initial ECG date. Time to repeat ECG for each period was calculated and compared using the Kruskal-Wallis test. To evaluate similarity between computer-generated and manual ECG, an intraclass correlation coefficient (ICC) was calculated among patients with any QTc interval exceeding 450 ms. In those with marked QTc-prolongation that had a dose-reduction, we determined whether the change in dose and QTc interval were linearly related. Clinical interventions performed among patients with marked QTc-prolongation were tabulated and mean change from peak to final QTc interval values assessed. QTc interval changes from initial measurement were analyzed with demographics (age, sex), clinical characteristics (cardiovascular disease, hypertension, and liver disease), pretreatment QTc interval, and methadone dose as covariates in a mixed effects model.

RESULTS

During the study period a total of 953 unique patients were enrolled, among whom 568 (60%) had at least one ECG tracing performed, and 531 were new entrants. Among new entrants, 436 (82%) underwent ECG and 143 (27%) had > 1 ECG tracing performed. A total of 186 (35%) new entrants had pretreatment ECG, 68 (37%) of whom had follow-up ECG performed. The distribution of patients with a decrease or increase in Bazett's-corrected QT interval is depicted in Figure 1. Most experienced an increase (69%) in QTc-interval on methadone, while 31% had a decrease. This in part reflected under-correction using Bazett's

formula since only 22% of patients experienced a decrease in QTc-interval using the Fridericia formula. Overall, the mean (SD) pretreatment QTc interval was 433.7 (16) ms, which increased to 449.2 (23) after methadone induction, representing an increase of 15.4 (25) ms ($p<0.0001$). This resulted in 16 and 2 patients exceeding the 450 and 500 ms thresholds respectively. The clinical and demographic characteristics of the overall cohort with ECG, stratified by QTc interval range, are shown in Table 1. The median time to follow-up ECG over the course of the study was 43 days, which decreased significantly over time from a median of 101 to 29 days ($p <0.0001$) among those with pretreatment and follow-up ECG (Figure 2).

A total of 864 ECG tracings were manually adjudicated, and 350 (40.5%) demonstrated a QTc interval > 450 ms. In comparing manual and computer-generated ECG, there were 6 changes in heart rate and 9 changes in the QTc interval among 7 of 568 (1.2%) patients. The ICC between computer-generated and manually-derived values was 0.83. A total of 6 (0.7% of ECGs examined) of these changes shifted the QTc interval value above or below the 500 ms threshold.

Similar to prior reports in the OTP setting,[17,18] 21 of the 568 patients (3.7%) screened had at least one QTc interval exceeding 500 ms. In the 21 patients in the overall cohort with a QTc interval exceeding 500 ms, a mean reduction in QTc interval from peak to final ECG [−55.5 ms, 95% CI (−77.0 to −33.9 ms), $p=0.001$] was observed, and 12 of 21 (57.1%) dropped below 500 ms at the final visit. In total, 16 of 21 patients (76.2%) had at least one clinical intervention performed, while 10 (62.5%) received more than one intervention. Overall, there were 32 unique interventions to mitigate arrhythmia risk including 9 patients who had a methadone dose reduction. On another 9 occasions, dose-escalation was halted. Concomitant QTc-prolonging medications were discontinued in 2 patients, and counseling to eliminate illicit drugs known to prolong the QTc interval (cocaine, alcohol) was provided in 8 instances. A total of 4 patients were transitioned to buprenorphine due to QTc-prolongation. No patients were denied opioid replacement therapy.

Among the 9 patients with marked QTc-prolongation in whom a methadone dose-reduction was performed (mean decrease, 22 mg/day), a correlation between the change in dose and change in QTc interval was observed ($R^2 = 0.20$, $p=0.057$, $df =18$) though it did not achieve statistical significance. Hypertension, cardiovascular disease and methadone dose were associated with a QTc interval >500 ms in the overall cohort. Among new entrants, no clinical or demographic covariates including age, sex, cardiovascular disease, hypertension, or liver disease were significantly correlated with the change in QTc interval in the mixed effects model. However higher methadone dose ($p=0.009$) and lower pretreatment QTc interval ($p<0.0001$) were significantly associated with a greater magnitude of increase in the QTc interval from baseline.

DISCUSSION

This pilot study illustrates the feasibility of initiating an ECG-based cardiac safety program despite minimal institutional resources. Although not all program components suggested by the SAMHSA expert panel[8,14] were implemented, this is to our knowledge the first

demonstration of an ECG-based intervention implemented in a community-based OTP setting in response to national guidelines. Our experience provides evidence that such a program results in a reduction in the QTc interval among those patients who develop marked QTc-prolongation. We found no evidence that program implementation resulted in treatment termination or impaired access to care.

The current study is among the largest to evaluate arrhythmia risk in the OTP setting. In this unselected cohort, we found that computer-generated QTc interval measurements correlated with manual over-reads similar to a previous prospective study.[19] The majority of ECG discrepancies (66%) resulted from gross misinterpretation of heart rate, a finding that can be easily identified by a discordant pulse and ventricular rate on ECG. The finding that < 1% of ECG tracings were adjudicated above or below the critical 500 ms threshold, where the risk of drug-induced torsade de pointes is most likely to occur,[20] supports current recommendations that computer-generated ECG is an appropriate diagnostic strategy.[8,14]

Results of our investigation are consistent with a previous cross-sectional analysis of on-site QTc interval screening[21] that did not incorporate an actual cardiac safety intervention. The study included 55 patients in whom baseline and one-year ECG was obtained. Overall, 6% developed a QTc interval >500 ms, a proportion similar to the current and previous OTP studies.[17–19] Albeit smaller in scope, this corroborates the feasibility of systematically implementing ECG in the OTP setting. Other authors have reported that methadone patients were less likely to comply with off-site ECG performance, reinforcing the importance of ECG screening within the OTP itself.[22]

A number of objections to universal ECG in OTPs have been raised including costs and the potential to limit access to care.[9–11,23] However, the primary scientific argument against universal ECG is predicated on the assumption that patients likely to develop torsade de pointes can be reliably identified by their clinical risk factor profile.[14,15] Prior reports have suggested that illicit drugs,[21] methadone dose,[24] and comorbidities[25] are associated with QTc-prolongation, which would support a risk factor-based approach to arrhythmia prevention. However, other than the QTc interval and methadone dose, we were unable to identify any baseline clinical risk factors independently associated with the magnitude of the change in QTc interval. Both the magnitude of the QTc interval change from baseline and the frequency of crossing an absolute QTc threshold of > 500 ms are considered essential regulatory metrics for proarrhythmic drug liability.[26] We observed that subjects with lower baseline QTc values exhibited a higher QTc increase at follow-up, suggesting that the change in QTc could be considered by clinicians in addition to evaluating absolute QTc thresholds. Our finding that lower baseline QTc is associated with a larger magnitude change is consistent with regulatory QTc studies among patients without structural heart disease.[26]

With regard to the magnitude change in QTc interval from baseline, one prospective study demonstrated a mean increase of 34 ms during methadone-maintenance.[18] Similar to our study, a pooled analysis suggests that methadone increased mean QTc, by 15 ms at doses of 120 mg/day.[27] Another Ik_r–blocking drug, sotalol, leads to a similar (10–40 ms) increase in mean QTc interval.[28] Presently, the package insert for methadone mentions QTc-

prolongation and advocates “careful monitoring of cardiovascular status, including QTc-prolongation and dysrhythmias”, but provides no clear recommendations regarding ECG.[29] By contrast, QTc-prolonging drugs such as droperidol and sotalol carry specific instructions regarding universal ECG monitoring.[28,30] Given increasing reports of torsade de pointes associated with methadone,[7] QTc interval monitoring in methadone treatment would be commensurate with the labeling of other marketed Ik_r-blocking drugs.

A number of study limitations merit consideration. Most importantly, this is a pilot implementation study without dedicated resources, whereby only a portion of patients received pre-treatment ECG. Although we targeted a goal of performing repeat ECG within 30-days of methadone initiation, this benchmark was not achieved until the end of the study. Because clinical algorithms for dose-adjustment and medication changes were not utilized, program effectiveness in reducing the QTc interval among high-risk patients was likely diminished. Patient education materials, satisfaction surveys, and formal physician training were not provided. Drug interactions were not quantitated; however, physician interventions addressing drug interactions were tabulated among those with marked QTc-prolongation as recommended.[8,14] We were unable to quantify the exact contribution of any single clinical action taken for marked QTc-prolongation on arrhythmia risk mitigation since the majority had more than one clinical action taken.

Not all patients in our cohort with marked QTc-prolongation achieved a reduction in QTc interval below the 500 ms threshold on subsequent ECG. This suggests that a system as implemented in this pilot study is likely to decrease, but not eliminate, the risk of torsade de pointes during long-term methadone treatment. Although the current study was large, it was underpowered to discern weak clinical predictors of QTc-prolongation, and a substantially larger sample would be required to ascertain the true impact of any ECG-based program on arrhythmia incidence. For example, if 4% of patients develop marked QTc-prolongation (>500 ms) as observed in the current study, and projecting an annual arrhythmia incidence of 5%, 13,000 patients would be required to detect a 50% reduction in arrhythmia events over 2-years with 80% power. In conclusion, our study supports a population-based ECG monitoring approach rather than a targeted comorbidity-based approach. Broader replication of an ECG-based cardiac safety program among OTPs to confirm our single center experience seems warranted.

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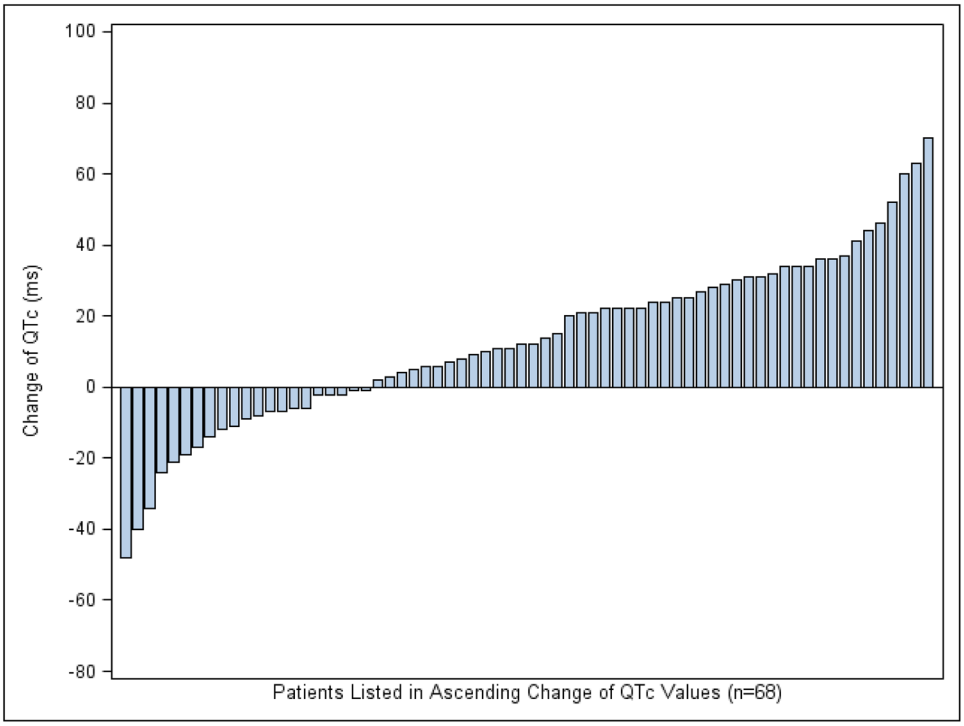

Figure 1.
QTc Interval Changes from Baseline to Follow-up.

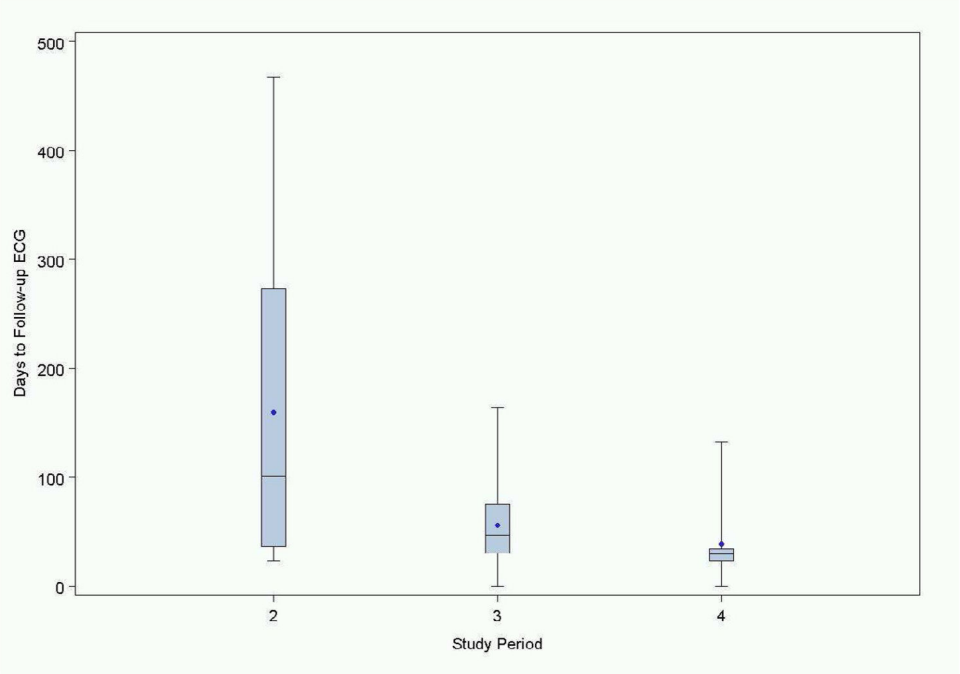

Figure 2.

Time to Follow-Up ECG in Patients with a Pretreatment ECG. The dot represents the mean number of days to ECG; the middle bar represents the median. The minimum, maximum, 25th and 75th percentiles are depicted with the boxplots. Period 1 is 9/1/09–2/28/10, Period 2 is 3/1/10–8/31/10, Period 3 is 9/1/10–2/28/11, and period 4 is 3/1/11–8/31/11. No newly enrolled patients had a pretreatment ECG during Period 1 of the study. Median days to follow-up ECG during periods 2–4 were 101, 47, and 29 days respectively ($p< 0.0001$ using ranked data and linear regression).

Table 1

Demographic and Clinical Characteristics of Patients with At Least One Electrocardiogram Prior to Intervention

Variable[a]	All Patients (n = 568)	QTc 450 – 499 ms (n = 195)	QTc ≥ 500 ms (n = 21)	P value[b]
Age, mean (SD) (Years)	41.2 (13.1)	43.6 (12.3)	47.6 (15.1)	0.1633
Male	322 (56.7%)	95 (48.7%)	11 (52.4%)	
Female	242 (42.6%)	97 (49.7%)	10 (47.6%)	
Hispanic/Latino	167 (29.4%)	56 (28.7%)	9 (42.9%)	0.2118
Black/African American	24 (4.2%)	5 (2.6%)	1 (4.8%)	0.4627
American Indian/Alaska Native	7 (1.2%)	4 (2.1%)	0 (0.0%)	1.0000
White	364 (64.1%)	129 (66.2%)	9 (42.9%)	0.0535
Other Race[c]	4 (0.7%)	0 (0.0%)	2 (9.5%)	0.0090
Cardiovascular Disease[d]	13 (2.3%)	9 (4.6%)	4 (19.0%)	0.0267
Diabetes Mellitus	2 (0.4%)	1 (0.5%)	1 (4.8%)	0.1854
Hypertension	63 (11.1%)	50 (25.6%)	12 (57.1%)	0.0044
Hypokalemia[e]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0
Liver Disease[f]	93 (16.4%)	75 (38.5%)	12 (57.1%)	0.1067
Human Immunodeficiency Virus	3 (0.5%)	3 (1.5%)	0 (0.0%)	1.000
Medications				
QTc prolonging drugs[g]	7 (1.2%)	6 (3.1%)	0 (0.0%)	1.000
Benzodiazepines	4 (0.7%)	4 (2.1%)	0 (0.0%)	1.000
Psychiatric drugs	7 (1.2%)	6 (3.1%)	0 (0.0%)	1.000
Antihypertensive/Diuretics	12 (2.1%)	8 (4.1%)	3 (14.3%)	0.0786
Baseline Data, mean (SD)				
QTc interval (ms)	439.5 (28.3)	458.2 (19.6)	499.0 (57.3)	NA
Methadone Dose (mg)	44.0 (46.3)	50.9 (49.7)	82.5 (53.6)	0.0065

[a] Percentages are based on total number of patients (n) in each group

[b] QTc = 450–499 ms and QTC>500 ms groups were compared by applying t-tests for age (test statistic t=−1.4, degree of freedom=214), and baseline dose (t=−2.75, degree of freedom=213). Fisher's exact tests were used to compare categorical variables.

[c] Participants could self-select more than one race and ethnicity resulting in percentages not totaling 100%.

[d] Includes coronary artery disease, myocardial infarction, and heart failure.

[e] Serum potassium < 3.0 mEq/L

[f] Includes Hepatitis C virus seropositivity

[g] Includes anti-emetics, antibiotics, antidepressants, antipsychotics obtained from a dynamic registry of QTc-prolonging drugs [20]