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QTc Prolongation in Veterans With Heroin Dependence on Methadone Maintenance Treatment

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Background: QTc prolongation and Torsade de Ppointes have been reported in patients on methadone maintenance.
Objectives: In this study, QTc was compared before and after the veteran (n = 49) was on a stable dosage of methadone for 8.72 ± 4.50 years to treat heroin dependence. Risk factors were correlated with the QTc once the veteran was on a stable dose of methadone. Differences in the clinical risk factors in subgroups of veterans with below and above mean QTc change was compared.
Patients and Methods: ECG data was obtained from a 12-lead electrocardiogram (pre-methadone and on methadone) on 49 veterans. Data and risk factors were retrospectively collected from the medical records.
Results: The mean QTc at baseline (pre-methadone) was 426 ± 34 msec and after being on methadone for an average of 8.72 ± 4.50 years was significantly higher at 450 ± 35 msec. No significant relationships were found between QTc prolongation and risk factors except for calcium. The methadone dosage was significantly higher in veterans with a QTc change above the mean change of ≥ 24 msec (88.48 ± 27.20 mg v.s 68.96 ± 19.84 mg). None of the veterans experienced cardiac arrhythmias.
Conclusions: The low complexity of medical co-morbidities may explain the lack of a significant correlation between any risk factor with the QTc except calcium and methadone dosage. The absence of TdP may be explained by the low prevalence of QTc values > 500 msec as well as the retrospective design of the study. During long-term methadone treatment, there was a slight increase in the QTc interval but we did not find evidence of increased cardiac toxicity as a reason for treatment termination.

Keywords: Opiate Substitution Treatment; Heroin Dependence; Arrhythmia; Torsades de Pointes

1. Background

Since the advent of methadone maintenance programs, there has been an overall increase in the life expectancy of heroin users (1). Methadone, a mu-receptor agonist, is a synthetic opiate that is commonly used in the treatment of opiate dependence (1). However, there are concerns regarding the disturbance of cardiac rhythm among individuals receiving methadone maintenance treatment, e.g., Torsade de Ppointes (TdP) secondary to rate-corrected QT interval prolongation (QTc) (1-3). There are many proposed thresholds for determining the value at which the QTc is considered prolonged; however, international regulatory guidelines suggest a sex-independent categorical threshold for QTc of 450 msec as a risk factor for TdP (1). However, the low prevalence of TdP precludes using QTc prolongation alone to determine the risk of developing this condition (4). Arrhythmias are more likely to occur if drug-induced QTc prolongation co-occurs with other risk factors for QT prolongation, such as the presence of congenital long QT syndromes, heart failure, bradycardia, electrolyte imbalances (hypokalemia, hypomagnesaemia, hypocalcaemia, hypophosphatemia), female sex, advanced age, hepatic impairment, slow metabolization of methadone, concomitant use of a QTc-prolonging drug, cytochrome P-450 inhibitors such as selective serotonin reuptake inhibitors, antiretroviral medications and antipsychotic medications (5, 6). Justo and colleagues found that the most prevalent risk factors for QTc prolongation were high-dose methadone (mean methadone dose was 231 ± 201 mg/day), drugs such as fluconazole and fluvoxamine that increase serum methadone levels, HIV infection, hypokalemia, female sex, liver cirrhosis, and cardiovascular disease (7).

2. Objectives

The aim of this study was to examine changes in the QTc duration before and after being on stable methadone treatment in veterans with heroin dependence and to assess QTc with risk factors such as methadone dosage, age, hypokalemia, hypocalcaemia, hypomagnesaemia, hypo-

phosphatemia, systolic congestive heart failure, hepatic cirrhosis, antidepressant medication use, antipsychotic medication use, other QTc prolonging medications and gender, both independently and as a group, in a veteran patient population on a stable dose of methadone for opiate dependence (5-8). The relationship between the above risk factors as a group and the change in the mean QTc post-methadone was also analyzed. Differences in the clinical risk factors for veterans with a QTc change $\geq$ 24 msec were compared to those with a QTc change $<$ 24 msec after being on methadone for an average of 8.72 $\pm$ 4.50 years.

3. Patiants and Methods

3.1. Participants

The McGuire VAMC Opioid Agonist Treatment program provides integrated services to veterans with opiate dependence. At the time of the study, 47 male and 2 female veterans were receiving methadone maintenance treatment. All of the 49 veterans meet DSM-IV criteria for heroin dependence (9). In this clinic, methadone liquid is administered at different dosages based on the veteran's needs. At every methadone visit, an observed urine drug screen is performed. Initially, the veterans come into the methadone clinic daily for at least 90 days to pick up their daily dose of methadone. For every 90 negative urine drug screens, the veteran will get one extra take home dose of methadone. On average, veterans receive a 14-day supply of methadone at each visit, which translates to 1260 negative consecutive drug screens. For a positive urine drug screen, the veteran will lose methadone take home privileges. 3 positive urine drug screens usually result in termination from the clinic. Comprehensive metabolic profiles and electrocardiograms were collected on admission to the program and yearly thereafter. Veterans with severe cardiopulmonary and liver disease were excluded from methadone maintenance treatment.

3.2. Procedures

The McGuire Veterans Hospital Institutional Review Board (IRB) approved our retrospective study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Opiate dependence was defined using the DSM-IV criteria (9). All veterans enrolled in the methadone maintenance treatment program undergo routine laboratory analyses. From retrospective chart review, the most recent clinical data available after being on methadone was collected on all 49 veterans enrolled in the methadone maintenance program at the time of the study. Clinical data included 12-lead electrocardiograms and risk factors for QTc prolongation such hypokalemia, hypocalcaemia, hypomagnesaemia, hypophosphatemia, methadone dose, age, gender, systolic congestive heart failure, hepatic cirrhosis, antidepressant medication use, antipsychotic medication use, and the use of other QTc prolonging medications such as levofloxacin, atazanavir/ritonavir, efavirenz, diltiazem, ciprofloxacin, trimethoprim-sulfamethoxazole, azithromycin and vardenafil. Additional clinical data collected included full time employment status, race, substance use disorder comorbidity, psychiatric disorder comorbidity and body mass index. Electrocardiogram data prior to starting methadone was also collected on all 49 veterans.

3.3. Clinical Variables

The QTc prior to initiating methadone treatment and the most up-to-date risk factors for QTc prolongation were correlated with the most recent QTc once the veteran had been on a stable dose of methadone. The QT interval was corrected for the heart rate using Bazett's formula, $QTc = QT \sqrt{RR}$ (10). Hypokalemia was defined as a potassium level of less than 3.5 mEq/L; hypocalcaemia was defined as a calcium level of less than 8.5 mg/dL; hypomagnesaemia was defined as a magnesium level of less than 1.5 mg/dL; and hypophosphatemia was defined as a phosphorous level of less than 2.5 mg/dL. Systolic congestive heart failure was defined as having an ejection fraction less than 45%. Hepatic cirrhosis was defined as having ultrasound imaging or a liver biopsy showing hepatic fibrosis as well as documentation confirming the diagnosis of cirrhosis. Other QTc prolonging medications included levofloxacin, atazanavir/ritonavir, efavirenz, diltiazem, ciprofloxacin, trimethoprim-sulfamethoxazole, azithromycin and vardenafil. All statistical analyses were calculated using IBM SPSS software (11). QTc was correlated with risk factors as a dichotomous variable at 450 msec and as a continuous variable. The P-Value was set at ≤ 0.05. Continuous variables (methadone dosage and age) were independently correlated with a dichotomized QTc using a Point bi-serial correlation and a continuous QTc using a Pearson correlation. Ordinal variables (hypophosphatemia, hypocalcaemia, hypokalemia, hypomagnesaemia, systolic congestive heart failure, liver cirrhosis) were independently correlated with a dichotomous and continuous QTc through Kendall's tau correlations. Dichotomous variables (gender, antidepressant use, antipsychotic use, other QTc prolonging medications) were correlated with a dichotomized QTc based on the Phi Coefficient and the continuous QTc based on a Pearson's correlation. Multivariate ANOVA was performed to correlate the clinical risk factors (phosphate, calcium, potassium, magnesium, systolic heart disease, hepatic cirrhosis, methadone dose, age, gender, use of antidepressant, use of antipsychotic medication, use of other QTc prolonging medications) as a group with the QTc as well as with the mean change in the QTc after 8.72 $\pm$ 4.50 years of Methadone Maintenance Treatment. A chi square and independent t-test was performed to analyze the difference in the clinical risk factors (phosphate, cal-

cium, potassium, magnesium, systolic heart disease, hepatic cirrhosis, gender, use of antidepressant, use of antipsychotic medication, use of other QTc prolonging medications, methadone dose, age) between those veterans with a QTc change ≥ 24 msec and those with a QTc change < 24 msec after being on methadone for 8.72 ± 4.50 years. A change in the QTc of ≥ 24 msec was used to separate the veterans into two separate groups because the mean change in the QTc after being on a stable dose of methadone for all veterans was 24 msec.

4. Results

All the 49 veterans were receiving methadone maintenance for heroin dependence (Table 1). The mean QTc (± SD) prior to initiating methadone treatment was 426 ± 34 msec. The most recent EKG had been obtained after having been on a stable dose methadone for an average (± SD) of 8.72 ± 4.50 years. The mean QTc (± SD) after being on methadone for 8.72 ± 4.50 years was 450 ± 35 msec.

Table 1. Sociodemographic Characteristics of the Sample (n = 49) [a]

Variable	Frequency
Age, y	56.96 ± 6.48
Body Mass Index, Kg/m^2	29.63 ± 6.61
Gender	
Male	47 (96)
Female	2 (4)
Race/Ethnicity	
Caucasian	11 (22)
African American	38 (78)
Full Time Employment	17 (35)
Substance Use Disorder Comorbidity	
None	5 (10)
Alcohol	2 (4)
Cocaine	14 (29)
Nicotine	8 (16)
Marijuana	2 (4)
Multiple	18 (37)
Psychiatric Disorder Comorbidity	
Post-Traumatic Stress Disorder	18 (37)
Major Depressive Disorder	3 (6)
Depressive Disorder Not Otherwise Specified	7 (14)
Attention Deficit Hyperactivity Disorder	1 (2)
Substance-Induced Mood Disorder	3 (6)
Multiple Diagnosis (≥ 2)	4 (8)

[a] Data are presented as No. (%) or Mean ± SD.

4.1. Overall Effect of Methadone on the QTc

A paired t-test showed that the mean increase in the QTc (24 msec) after being on methadone treatment for an average of 8.72 ± 4.50 years was statistically significant (t = -4.62, df = 46, P < 0.01).

4.2. Prevalence of Risk Factors for QTc Prolongation and TdP

Methadone Dose: The mean dose of methadone (± SD) prescribed was 78.20 ± 25.30 mg/day. QTc prolongation: On admission to the methadone maintenance treatment program, 40 veterans (82 %) displayed a QTc less than or equal to 450 msec, while 9 (18%) displayed a QTc greater than 450 msec. 4 veterans had a QTc between 450 to 475 msec, 3 veterans had a QTc between 475 msec and 500 msec, 1 veteran had a QTc between 500 msec and 525 msec, 1 veteran had a QTc between 525 msec and 550 msec. The average heart rate (± SD) was 72.00 ± 11.81 bpm. After being on methadone for an average of 8.72 ± 4.50 years, 26 (53%) veterans displayed a QTc of less than or equal to 450 msec, while 23 (47%) exhibited a QTc greater than 450 msec. 19 veterans had a QTc between 450 msec and 475 msec; 2 veterans had a QTc between 475 msec and 500 msec; 1 veteran had a QTc between 500 msec and 525 msec; 3 veterans had a QTc between 525 msec and 550 msec. The average heart rate (± SD) was 70.00 ± 12.89 bpm.

TdP: Despite the fact that 47% of the participants presented a QTc greater than 450 msec post methadone, none of the participants experienced any arrhythmias. Psychotropic Medications: 24 (49%) were on an antidepressant medication; and 4 (8%) were on an antipsychotic medication.

Electrolytes: 6 (12%) veterans were hypokalemic, 11 (22.45%) had hypocalcaemia while 10 (20%) had hypomagnesaemia, and 1 (2%) had hypophosphatemia. Co-morbid physical disorders: 13 (26.53%) had cirrhosis, 2 (4.08%) had systolic congestive heart failure.

4.3. Effect of Risk Factors on the QTc After Initiating Methadone

Point-biserial correlations revealed no significant association between the dichotomized QTc and methadone dosage (r = 0.19, P = 0.19) or age (r = 0.17, P = 0.24). Pearson's correlation revealed no significant correlation between the continuous QTc and methadone dosage (r = 0.18, P = 0.22) or age (r = 0.17, P = 0.24). Kendall's Tau correlations did not indicate any significant association between dichotomized QTc and potassium (τ = -0.18, P = 0.20), magnesium (τ = -0.11, P = 0.48), phosphate (τ = -0.15, P = 0.33), systolic heart failure (τ = 0.225, P = 0.06) or cirrhosis (τ = -0.20, P = 0.09). However, Kendall's Tau correlations did indicate a significant association between dichotomized QTc and calcium (τ = -0.35, P = 0.02). Similarly, Kendall's Tau correlations did not show any significant correlations between continuous

Table 2. Case Report Risk Factors for QTc Interval Prolongation and Torsade de Pointes (TdP) in Descending Order of the Change in the QTc on a Stable Dose of Methadone

Case #	Current risk Factors Other Than Methadone	Change in QTc, msec	Pre methadone QTc, msec	On a stable dose of methadone QTc, msec	Methadone daily dose, mg	Age, y
#38	hypo-mg++	122	398	520	85	56
#21	none	108	430	538	90	61
#23	quetiapine	96	453	549	120	61
#3	venlafaxine	79	377	456	100	41
#32	none	75	401	476	85	52
#41	bradycardia, citalopram	68	387	455	120	60
#31	hypo-K+, hypo-ca++, trazodone	60	412	472	90	59
#9	trazodone	58	390	448	65	55
#28	sertraline, trazodone	55	403	458	55	56
#7	paroxetine	55	402	457	100	59
#19	hypo-ca++, azithromycin	51	401	452	110	59
#48	bradycardia, diltiazem	51	400	451	45	64
#40	none	45	399	434	80	53
#45	hypo-mg++, hypo-ca++, amitryptiline	41	433	474	60	55
#36	hepatic cirrhosis, hypo-mg++, azithromycin, ciprofloxacin, trimethoprim sulfamethoxazole, trazadone	40	410	450	85	51
#44	female, hypo-K+, bradycardia, venlafaxine	36	394	430	70	50
#12	risperidone, levofloxacin, trazodone	35	436	471	175	55
#20	none	28	424	452	70	61
#43	hepatic cirrhosis	28	422	450	65	64
#2	hepatic cirrhosis, hypo-Mg++, trazodone	28	418	446	85	60
#27	hepatic cirrhosis	28	394	422	100	61
#30	hypo-Ca++	24	400	424	80	59
#17	hepatic cirrhosis	24	396	420	100	62
#29	none	23	382	405	95	39
#46	hypo-po43-, hypo-ca++, hepatic cirrhosis, azithromycin, trazodone	21	439	460	50	53
#35	hepatic cirrhosis, hypo-mg++, hypo-ca++, sertraline	20	431	451	100	62
#33	levofloxacin, hypo-ca++	19	479	498	55	63
#11	hypo-ca++, systolic heart failure	15	451	466	70	75
#5	hypo-k+, hypo-mg++, bradycardia, sertraline	14	431	445	80	61
#14	hypo-ca++, amitriptyline	14	413	427	55	63
#26	bradycardia	12	398	410	70	59
#18	atazanavir, ritonavir	8	424	432	60	56
#13	hepatic cirrhosis, quetiapine, sertraline	6	436	442	100	59
#6	hypo-k+	4	470	474	75	58
#37	bradycardia	1	398	399	70	54
#22	hepatic cirrhosis, systolic heart failure, hypo-k+, hypo-mg++, hypo-ca++, trazodone	0	536	536	60	57
#42	hypo-k+, trazodone	0	459	459	90	51
#25	female	0	439	439	55	50
#8	hepatic cirrhosis, mirtazapine	0	434	434	55	54
#4	bradycardia	0	428	428	80	64
#34	sertraline, hepatic cirrhosis	0	416	416	45	61
#49	hypo-Mg++	0	403	403	50	55
#39	vardenifil	-3	445	442	60	60
#16	none	-13	409	396	90	55
#47	efavrienz, trazodone	-15	416	401	100	57
#15	hepatic cirrhosis, hypo-Mg++, trazodone	-22	484	462	70	57
#24	mirtazapine, bradycardia	-29	438	409	30	55
#10	none	-56	499	443	90	37
#1	hypo-mg++, hypo-ca+, quetiapine, nortriptyline	-64	519	455	40	62

QTc and potassium (τ = 0.11, P = 0.35), magnesium (τ = 0.06, P = 0.62), phosphate (τ = -0.14, P = 0.25), systolic heart failure (τ = 0.22, P = 0.07) or cirrhosis (τ = -0.08, P = 0.52). However, Kendall's Tau correlations did show a significant correlation between the continuous QTc and calcium (τ = -0.25, P = 0.05). The phi coefficient did not show any significant association between the dichotomized QTc and gender (ϕ = -0.19, P = 0.17), antidepressant use (ϕ = 0.14, P = 0.32), antipsychotic use (ϕ = 0.17, P = 0.24), and other QTc prolonging medications (ϕ = 0.09, P = 0.53). The Pearson's correlation did not show any significant correlation between the continuous QTc and gender (r = -0.09, P = 0.53), antidepressant use (r = -0.06, P = 0.69), antipsychotic use (r = 0.26, P = 0.07) and other QTc prolonging medications (r = -0.02, P = 0.87).

4.4. Effect of the Risk Factors as a Group on the QTc After Initiating Methadone

Multivariate ANOVA did not show a significant correlation between the risk factors as a group (methadone dosage, age, hypokalemia, hypocalcaemia, hypomagnesaemia, hypophosphatemia, systolic congestive heart failure, hepatic cirrhosis, antidepressant medication use, antipsychotic medication use, other QTc prolonging medications, and gender) and the continuous QTc (F = 1.18, df = 12, P = 0.34).

4.5. Effect of the Risk Factors as a Group on the Change in the QTc After Initiating Methadone

Multivariate ANOVA did not show a significant correlation between the risk factors as a group (methadone dosage, age, hypokalemia, hypocalcaemia, hypomagnesaemia, hypophosphatemia, systolic congestive heart failure, hepatic cirrhosis, antidepressant medication use, antipsychotic medication use, other QTc prolonging medications, gender) and the mean change in the QTc (F = 1.78, df = 12, P = 0.10).

4.6. Difference in the Clinical Risk Factors Between Veterans With a Change of QTc ≥ 24 Msec and Those With a QTc < 24 Msec

A chi-square did not show any significant differences in antidepressant use (χ 2 = 0.18, df = 1, P = 0.67), antipsychotic use (χ 2 = 0.02, df = 1, P = 0.90), other QTc prolonging medication (χ 2 = 0.05, df = 1, P = 0.84), gender (χ 2 = 0.01, df = 1, P = 0.93), hypocalcaemia (χ 2 = 0.91, df = 1, P = 0.34), hypomagnesaemia (χ 2 = 0.28, df = 1, P = 0.60), hypophosphatemia (χ 2 = 1.18, df = 1, P = 0.28), hypokalemia (χ 2 = 1.20, df = 2, P = 0.55) systolic congestive heart failure (χ 2 = 1.84, df = 1 P = 0.18) and hepatic cirrhosis (χ 2 = 0.50, df = 1, P = 0.48) between the 2 groups of veterans. An independent t-test did not show a significant difference in age between the 2 groups of veterans (t = -0.17, df = 47, P = 0.86). The mean dose of methadone prescribed for veterans (88.48 ± 27.20 mg) with a change in QTc ≥ 24 msec was significantly higher than the mean dose of methadone (68.96 ± 19.84 mg) prescribed for veterans with a change in QTc < 24 msec (t = 2.82, df = 45 P = 0.01).

5. Discussion

Males are highly over-represented in our veterans therefore our results should not be extrapolated to the general population.

5.1. Methadone-Associated QTc Prolongation

After being on a stable dose of methadone for 8.72 ± 4.50 years there was a statistically significant increase in the QTc (mean 24 msec). The modification of QTc during methadone maintenance does not seem to be progressive throughout the years. Our findings are consistent with those of Wedham and colleagues, who observed an increase in the QTc from baseline to 4 weeks, 8 weeks and 16 weeks in 23% of patients receiving methadone maintenance treatment with a normal QTc at baseline (12). In the present study, there was no significant association between QTc prolongation and the methadone dose similar to the findings of Roy and colleagues who found no significant correlation between the mean QTc of 420.9 ± 21.2 msec, and the mean daily dose of methadone, which was 80.4 ± 27.7 mg, in their patients receiving methadone maintenance treatment (13). In our study however, there was a significant difference in the methadone dosage between the groups with ≥ 24 msec increase in QTc and < 24 msec increase (88.48 ± 27.20 mg versus 68.96 ± 19.84 mg). But the relationship between methadone dosage, methadone blood level and QTc prolongation is unclear. A study by Peles and colleagues found that the dose of methadone and serum methadone levels did not correlate with QTc (14).

5.2. Age and QTc Prolongation

In general, the aging process is an independent risk factor for QTc prolongation and for the development of arrhythmias. The QTc may increase with age secondary to fibrosis and amyloidosis of the myocardium as well as cardiac hypertrophy and aortic impedance (15). However, similar to the present work, other studies have produced conflicting results regarding the relationship between age and the QTc. For example, Merri and colleagues quantified electrographic ventricular repolarization and found no relationship between age and the QT interval (16). Due to the narrow age range of our veteran population (56.96 ± 6.48 years), it was highly unlikely that we would find a significant correlation between age and the QTc. In addition, we did not explore the impact of other cardiovascular factors such as smoking status, which could affect the relationship between age and the QTc.

5.3. Gender and QTc Prolongation

Female gender appears be an independent risk factor

for QTc prolongation. Men exhibit shorter resting QTcs and are therefore less likely to develop TdP secondary to the influence of sex hormones on ventricular repolarization (17). A review of FDA databases performed by Ebert and colleagues found that a higher percentage of women compared to men developed TdP in response to a variety of drugs that share an ability to block potassium currents (18). Due to the low prevalence of females (n = 2) in our study population, it is highly unlikely that we would find a statistically significant difference between gender and the QTc.

5.4. Electrolytes and QTC Prolongation

Fluctuations in electrolytes can prolong the QTc. Hypokalemia, hypomagnesaemia, hypophosphatemia and hypocalcaemia have been associated with increased QTc (19-21). The lack of a significant negative correlation between hypokalemia, hypomagnesaemia or hypophosphatemia and the QTc observed in our study population can most likely be attributed to the lack of severe electrolyte abnormalities. Golzari and colleagues examined the effects of hypokalemia, hypocalcaemia and hypomagnesaemia on the QTc and observed that the prevalence of abnormal QTcs varied based on the applied criteria, ranging from 25.2%, when using the most lenient criteria (QTc $\geq$ 450 msec.), to 3.5%, when the most restrictive criteria were applied (QTc $\geq$ 500 msec.) (6). Although the QTc was dichotomized at 450 msec in our study, there was no significant negative correlation found between hypokalemia, hypomagnesaemia and hypophosphatemia. However, in our study there was a significant negative association between calcium and the dichotomized and continuous QTc. Hypocalcaemia has been shown to prolong the QT interval and that calcium replacement decreases the QT interval (22).

5.5. Drug Interactions and QTC Prolongation

Methadone is metabolized hepatically by N-demethylation via various cytochrome P450 isoforms (23). Therefore, administration of cytochrome P450 inhibitors, such as antidepressants and antipsychotics, will decrease the metabolism of methadone and enhance its effects, resulting in QTc prolongation (23). In addition, independent of cytochrome P450 inhibition, certain SSRIs and antipsychotics can prolong the QTc (24, 25). Selective serotonin reuptake inhibitors (SSRIs), as a class, are associated with QTc prolongation, with citalopram being the most likely to be associated with this phenomenon, especially at doses greater than 40 mg/day (23). In the present study, the lack of a significant correlation between antidepressants and the QTc can be attributed to the therapeutic doses of antidepressants used. Additionally, tricyclic anti-depressants (TCA's) have a higher rate of QTc prolongation compared to other anti-depressants classes (26). In our study, only 3 of the 24 veterans on an anti-depressant were being prescribed a TCA. Antipsychotics can also prolong the QTc; however, this effect differs based on the particular type of antipsychotic studied (25). Through analysis of 1,017 patients with schizophrenia, Ozeki and colleagues found that chlorpromazine, intravenous haldol and sultropride were associated with an increased QTc at therapeutic doses, whereas olanzapine, quetiapine, risperidone and zotepine were not associated with an increased QTc (25). In their study, the effect of ziprasidone on the QTc was not analyzed, which is notable because among the atypical antipsychotics, ziprasidone appears to be most likely to prolong the QTc (27). In the present study, the lack of a significant correlation between antipsychotics and the QTc can be attributed to the fact that none of the veterans was on chlorpromazine, intravenous haldol, sultropride or ziprasidone.

5.6. Medical Comorbidities and QTc Prolongation

Prolongation of the QTc is observed in a number of heart conditions, especially in association with structural heart defects such as heart failure (28). The absence of a significant association between systolic congestive heart failure and the QTc observed in our veteran population is most likely due to the low prevalence (4.08%) of veterans with systolic heart failure receiving MMT and the dynamic nature of the QT interval under heart failure. Hepatic disease, in particular liver cirrhosis, has been documented as a risk factor for QTc prolongation (29). QTc prolongation tends to be more severe in patients with alcoholic cirrhosis or Child-Pugh Class C cirrhosis (29). The absence of a significant association between cirrhosis and QTc in our study is due to none of the veterans having cirrhosis severe enough to be classified as Child-Pugh Class C.

The low incidence (0%) of cardiac arrhythmias observed in this study could be due to the fact that we were interested in and included only veterans who stayed in the methadone program for many years, the moderate dose of methadone prescribed (78.20 ± 25.30 versus 99 ± 49 mg/day) and the relatively low prevalence of electrolyte abnormalities and medical comorbidities (30). Thus veterans who were originally enrolled in the methadone maintenance program but left the program in the early stages of their treatment due to any reason are not included. Therefore including only veterans with long-term methadone treatment may have excluded those veterans with more severe QT prolongation or who may have left the program due to arrhythmias, early on. But epidemiological data do not support a correlation between methadone and substantial TdP mortality (31). We found that after being on methadone for an average of 8.72 ± 4.50 years, the QTc increased significantly by an average of 24 msec. The change in the QTc does not appear to be progressive throughout the years. The higher dose of methadone was the only clinical risk factor that significantly differentiated those veterans with a QTc change $\geq$ 24 msec versus

those veterans with a QTc change < 24 msec. The absence of a significant correlation observed between the risk factors except calcium and the QTc can be attributed to the low power of the study (n = 49) as well as the lack of severity and complexity among the assessed co-morbidities. Thus our data supports that methadone dose is a material factor in QTc increase but does not support the dose being a risk factor both independently or in combination with other risk factors for inducing TdP or polymorphic ventricular arrhythmias (PVA). Concern of increasing arrhythmias in patients on methadone has come mostly from case-reports, while many epidemiological studies have not shown a significant increase in arrhythmias (31). A review by the Cochrane group found no evidence to support the use of routine EKG monitoring for preventing arrhythmias in methadone maintained patients (32). The QTc thresholds for ventricular arrhythmias are not specific and a significant proportion of cardiac events occur at QTc values lower than 450 msec. During long-term methadone maintenance treatment, there was slight increase in the QTc interval but we did not find evidence of increased cardiac toxicity as a reason for treatment termination. A limitation of the study is the non-inclusion of veterans who were originally enrolled in the methadone maintenance program but left the program before the initiation of the study. Other limitations include the small cohort size.

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Authors' Contributions

Study concept and design: Hassamal, Fernandez, and Pandurangi. Analysis and interpretation of data: Hassamal and Rekabdarkolaee. Drafting of the manuscript: Hassamal. Critical revision of the manuscript for important intellectual content: Hassamal, Fernandez, and Pandurangi Statistical analysis: Hassamal and Rekabdarkolaee.

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