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Drug-induced torsades de pointes in an underserved urban population. Methadone: is there therapeutic equipoise?

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Abstract
Background Although it has been well established that methadone use can result in prolonged QTc/torsades de pointes (TdP) and has been labeled as one of the main drugs that cause TdP, it is still prescribed indiscriminately, and several cases of methadone-associated TdP have been seen in our community.
Methods Our objective was to determine the associated factors for prolonged QTc and the development of torsades de pointes (TdP) in our underserved patient population. We found 12,550 ECGs with prolonged QTc between 2002 and 2013. Medical records were reviewed in order to identify precipitating factors for prolonged QTc and to detect incidence of TdP.
Results We identified 2735 patients with prolonged QTc who met the inclusion criteria. Of these, 89 (3 %) experienced TdP. There was a greater prevalence of HIV infection in the TdP group (11.2 vs. 3.7 %, $p<0.001$). Furosemide, hydrochlorothiazide, selective serotonin reuptake inhibitors (SSRIs), amiodarone, ciprofloxacin, methadone, haloperidol, and azithromycin were the drugs most often associated with prolonged QTc (31, 8.2, 7.6, 7.1, 3.9, 3.4 and 3.3 %, respectively). However, the agents most commonly associated with TdP were furosemide (39.3 %), methadone (27 %), SSRIs (19.1 %), amiodarone (18 %), and dofetilide (9 %). The medications with statistical significance in the multivariate analysis for TdP development in descending order were as follows: ranolazine (odds ratios [OR]=53.61, 95 % confidence interval [CI] 5.4–524, $p<0.001$), dofetilide (OR=25, CI 6.47–103.16, $p<0.001$), voriconazole (OR=21.40, CI 3.24–124.25, $p<0.001$), verapamil (OR=10.98, CI 2.62–44.96, $p<0.001$), sotalol (OR=12.72, 1.95–82.81, $p=0.008$), methadone (OR=9.89, CI 4.05–24.15, $p<0.001$), and SSRI (OR=2.26, CI 1.10–5.96, $p<0.001$). This multivariate analysis revealed that amiodarone and HIV infection were not implicated in TdP.
Conclusion Methadone was by far the leading medication implicated in the development of TdP and an independent predictor in both univariate and multivariate analyses despite the fact that it was not the most common QT-prolonging medication in our population.

Keywords Methadone · Torsades de pointes · Prolonged QT

1 Background

Acquired prolonged QT syndrome is associated with life-threatening arrhythmias, predominantly torsades de pointes (TdP) [1]. Medications, including those which inhibit the cytochrome P450 enzymes, structural heart disease, cerebrovascular and coronary ischemia, electrolytes disturbances, connective tissue disease, thyroid disease, ion channel genetic mutations, hypoalbuminemia, and brady-arrhythmias are among the risk factors for development of prolonged QT/TdP. Female gender and increasing age are considered additional risk factors [1–3]. Drug-induced QT prolongation appears to be the most common cause of acquired prolonged QT syndrome and results primarily from blockade of a component of the delayed rectifier potassium current (IKr) channels, also known as HERG (human ether-a-go-go related gene) channel. This channel is profoundly involved in the repolarization phase of the action potential of cardiac myocytes [1, 4, 5].

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Methadone- and opioid-associated mortality rates are increasing across the United States. In 2005, drug overdose surpassed firearms as a cause of death. While total poisonings increased by 66 % from 1997 to 2005, methadone-related deaths increased by 468 % [6]. The only two drugs approved in the United States for the treatment of opioid abuse and dependence are methadone and buprenorphine [7, 8]. Methadone is a mu opiate receptor agonist and NMDA receptor antagonist (tenfold higher potency over morphine) prescribed to treat patients with heroin addiction as well as other opioids and to treat chronic pain. Although it has been well established that methadone use can result in prolonged QTc/TdP and has been labeled as one of the main drugs that cause TdP, it is still prescribed indiscriminately. This may be related to the difficulty in determining what the incidence and prevalence of prolonged QT/TdP in patients using these medications is, and that most of the literature is based on case reports or small observational series.

1.1 Study aim

The aim of this study was to determine what factors are associated prolonged QTc and the development of torsades de pointes in our unique patient population.

2 Methods

2.1 Study population

We conducted a single-center retrospective cohort study at Montefiore Medical Center, a large tertiary care center in the Bronx, New York. We analyzed over 12,550 ECGs with prolonged QTc using the MUSE ® Cardiology Information System between January 2002 and December 2013. Selection criteria included adult patients older than 18 years of age with an ECG demonstrating prolonged QTc (greater than 440 ms for men and 460 ms for women). After initial screening, duplicate ECGs, ECGs with paced or irregular rhythms (i.e., atrial fibrillation, multifocal atrial tachycardia), and ECGs obtained in the outpatient setting were excluded. QTc interval was measured manually with electronic calipers in every single patient included in the analysis. Subsequently, electronic medical records were reviewed for all patients who meet inclusion criteria.

2.2 Definitions. ECG analysis

A database was created with the ECGs, which manifested prolonged QTc. In order to validate the ECG software's accuracy in measuring QTc, we measured the QT interval with electronic calipers, from the onset of the QRS complex to the end of the T wave. This value was adjusted by gender, heart rate, and QRS duration as per the AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram. For our analysis, we used the ECG lead with the longest QT interval in which a prominent U wave is absent. Moreover, if the T wave and U wave were superimposed or could not be separated, the QT was measured by extending the downslope of the T wave drawing a tangential line to the steepest portion of the downslope until it crosses the TP segment [9]. Bazett's formula was used to calculate the QTc. QTc longer than 440 ms for men and 460 ms for women was considered abnormal. Once the cohort of patients was built, the medical records were reviewed in order to identify patient demographics, baseline characteristics, structural heart disease, known precipitating factor/factors for prolonged QTc, and dose of different medications to detect which patients actually had life-threatening arrhythmias especially TdP. For all patients who had TdP, the event was detected by telemetry, ECG cardiac monitors, or ECG recording. In addition, the electrophysiology team was consulted to confirm each event. ECGs performed before the event were analyzed if available. Figure 1 demonstrates the ECG and patient selection algorithm.

2.3 Statistical analysis

Baseline characteristics and risk factors known to cause QT prolongation were summarized using descriptive statistics, i.e., mean (SD) for continuous variables and frequency (percentage) for categorical variables. Continuous variables were compared using *t* test or nonparametric equivalent, and chi-square test was employed for comparison of categorical variables. Drugs that were associated with prolonged QT in our univariate analysis were then entered into a multivariate linear regression model, adjusted for hypokalemia, hypomagnesemia, HIV infection, coronary artery disease (CAD), cerebrovascular accident (CVA), and hypothermia. This assessment of association was adjusted for other known potential confounders such as concomitant QT-prolonging medications and inhibitors or inducers of cytochrome P450 3A4 (refer to the drug table above). Results were presented as adjusted regression coefficient of QTc prolongation with associated 95 % confidence interval and odds ratios was calculated. Statistical significance was claimed at a computed p-value ≤ 0.05. All analyses were performed on SPSS v21 (IBM, Armonk, NY).

3 Results

After analyzing 12,550 ECGs and excluding duplicates, irregular/paced rhythms, and outpatients, we identified 2735 patients (41 % male; mean age 63±15) with prolonged QTc (501±46 ms). Of these 2735 patients, 89 (3 %) experienced TdP. Baseline characteristics of patients

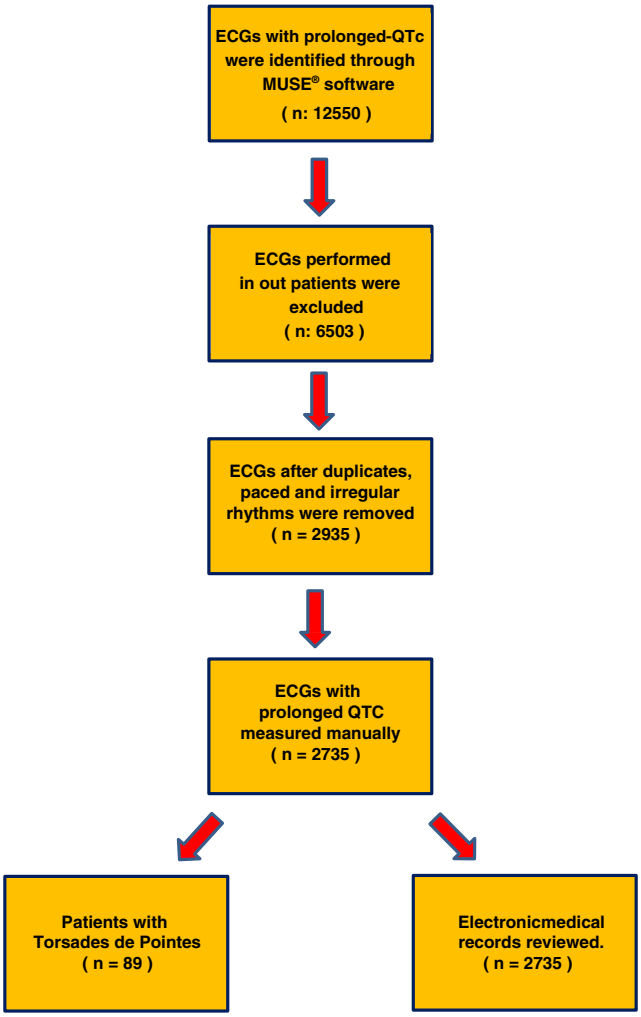

Fig. 1 Selection of ECGs and Patients

with prolonged QT and TdP are shown in Table 1. Patients who developed TdP had a significantly prolonged QTc at baseline (551 vs. 499 ms, $p<0.001$) and lower ejection fraction (47 vs. 55 %, $p<0.001$) compared to those who did not develop TdP. Prevalence of ischemic heart disease, stroke, and connective tissue disorders was similar. There was a greater percentage of patients with HIV infection in the TdP group (11.2 vs. 3.7 %, $p<0.001$). Hypokalemia and hypomagnesemia were more common in the TdP group [36 vs. 10.1 % ($p<0.001$) and 14.9 vs. 4.2 % ($p=0.01$), respectively]. Furosemide (31 %), hydrochlorothiazide (8.2 %), selective serotonin reuptake inhibitors (SSRIs) (7.6 %), amiodarone (7.1 %), ciprofloxacin (5.9), methadone (3.9 %), haloperidol (3.4 %), and azithromycin (3.3 %) were the drugs most often associated with prolonged QTc. Importantly however, the agents, which were most commonly associated with TdP, were furosemide (39.3 %), methadone (27 %), SSRIs (19.1 %), amiodarone (18 %), and dofetilide (9 %) (Fig. 2).

3.1 Univariate analyses

In our univariate analysis, longer QTc (OR 1.01, CI 1.01–1.01, $p<0.001$) and lower ejection fraction (OR 0.96, CI 0.95–0.98, $p<0.001$) remained significant predictors of TdP. Other predictors included HIV infection (OR 3.30, CI 1.66–6.56, $p<0.001$), hypokalemia (OR 5.00, CI 3.18–7.85, $p<0.001$), and hypomagnesemia (OR 3.962, CI 2.127–7.382, $p<0.001$). The medications with statistical significance in the univariate analysis in descending order based on odd ratios were as follows: ketoconazole (OR 62.85, CI 5.64–77.24, $p<0.001$), clarithromycin (OR 32.12, CI 7.90–130.63, $p<0.001$), voriconazole (OR 21.40, CI 5.93–77.24, $p<0.001$), ranolazine (OR 13.59, CI 3.45–53.46, $p<0.001$), dofetilide (OR 13.40, CI 5.73–31.34, $p<0.001$), levofloxacin (OR 10.45, CI 2.08–52.54, $p=0.004$), methadone (OR 8.98, CI 5.41–14.89, $p<0.001$), verapamil (OR 7.52, CI 2.47–22.83, $p<0.001$), sotalol (OR 6.96, 1.48–32.70, $p=0.014$), protease inhibitors (OR 5.52, CI 2.53–12.06, $p<0.001$), cocaine (OR 3.80, CI 1.58–9.11, $p=0.003$), SSRI (OR 2.88, CI 1.66–4.98, $p<0.001$), and amiodarone (OR 2.88, CI 1.64–505, $p<0.001$). Interestingly, furosemide and hydrochlorothiazide which were the two most common drugs associated with TdP were not independent predictors in the univariate analysis (Table 2).

3.2 Multivariate analysis

In our multivariate analysis, longer QTc and lower ejection fraction remained significant predictors of TdP. Another predictor was hypokalemia (OR 5.56, CI 2.9–10.68, $p<0.001$). The medications with statistical significance in the multivariate analysis in descending order based on odd ratios were as follows: ranolazine (OR 53.61, CI 5.4–524, $p<0.001$), dofetilide (OR 25, CI 6.47–103.16, $p<0.001$), voriconazole (OR 21.40, CI 3.24–124.25, $p<0.001$), verapamil (OR 10.98, CI 2.62–44.96, $p<0.001$), sotalol (OR 12.72, 1.95–82.81, $p=0.008$), methadone (OR 9.89, CI 4.05–24.15, $p<0.001$), and SSRI (OR 2.26, CI 1.10–5.96, $p<0.001$). This multivariate analysis revealed that amiodarone although a common cause of prolonged QT was not implicated in TdP (Table 3). Likewise, HIV infection was no longer an independent predicator of TdP.

4 Discussion

The primary drugs implicated in prolonged QT in our patient population were furosemide, hydrochlorothiazde (HCTZ), SSRIs, and amiodarone. However, although amiodarone was a common QT-prolonging drug, multivariate analysis did not show statistical significance for the development of TdP. This may be explained by its multiple ion channel interactions

Table 1 Baseline characteristics of patient with prolonged QTc and those who developed TdP in the hospital

	Prolonged QTc *n* or mean	*n*=2735 % or SD	TdP *n* or mean	*n*=89 % or SD	Total *n* or mean	% or SD	
Age	63	16	61	14	63	15	0.227
Male	1120	41	33	37.1	1153	40.8	0.465
Electrocardiogram							
Heart rate (bpm)	76	13.1	75.9	18.4	76	13.3	0.95
QT	448.7	56	489.2	47.1	449.9	56.2	<0.001
QTc (Bazzet)	499	44	551	84	501	46	<0.001
Ejection fraction	55	14	47	16	54	14	<0.001
Comorbidities							
Ischemia or infarction	792	29	29	32.6	821	29.1	0.458
Stroke	338	12.4	12	13.5	350	12.4	0.751
Connective tissue disorder	80	2.9	1	1.1	52	1.8	0.316
HIV	101	3.7	10	11.2	111	3.9	<0.001
Hypothermia	51	1.9	1	1.1	52	1.8	0.609
Medications							
Amiodarone	193	7.1	16	18	209	7.4	<0.001
Sotalol	9	0.3	2	2.2	11	0.4	0.004
Dofetilide (Tikosyn)	20	0.7	8	9	28	1	<0.001
Verapamil	17	0.6	4	4.5	21	0.7	<0.001
Ketoconazole	1	0	2	2.2	3	0.1	<0.001
Voriconazole	6	0.2	4	4.5	10	0.4	<0.001
Azithromycin	89	3.3	4	4.5	93	3.3	0.519
Clarithromycin	4	0.1	4	4.5	8	0.3	<0.001
Levofloxacin	6	0.2	2	2.2	8	0.3	<0.001
Haloperidol	94	3.4	2	2.2	96	3.4	0.542
SSRI	207	7.6	17	19.1	224	7.9	<0.001
Risperidone	41	1.5	2	2.2	43	1.5	0.571
HCTZ	223	8.2	7	7.9	230	8.1	0.979
Furosemide	859	31.4	35	39.3	894	31.7	0.114
Ranolazine	7	0.3	3	3.4	10	0.4	<0.001
Protease inhibitors	48	1.8	8	9	56	2	<0.001
Cocaine	51	1.9	6	6.7	57	2	0.001
Methadone	108	3.9	24	27	132	4.7	<0.001
Electrolytes							
Potassium (mEq/L)	4.1	0.57	3.71	0.56	4.09	0.57	<0.001
Magnesium (mg/dl)	2.07	0.41	1.96	0.48	2.07	0.41	0.001
Calcium (mg/dl)	8.78	0.88	8.76	0.91	8.78	0.88	0.881
Albumin (g/dl)	3.59	0.7	3.45	0.75	3.59	0.7	0.065
TSH	1.63	3.67	2.34	1.79	1.65	3.63	0.149
Electrolyte abnormalities							
Hypokalemia	269	10.1	32	36	301	10.9	<0.001
Hypomagnesemia	101	4.2	13	14.9	114	4.6	<0.001
Hypocalcemia	805	30.2	28	31.5	833	30.2	0.795
Hypoalbuminemia	611	25	26	29.5	637	25.2	0.339
Hypothyroidism	105	6.6	7	12.5	112	6.8	0.083

TdP torsades de pointes, *HIV* human immunodeficiency virus, *SSRI* selective serotonin reuptake inhibitors, *HCTZ* hydrochlorothiazde, *TSH* thyroid-stimulating hormone

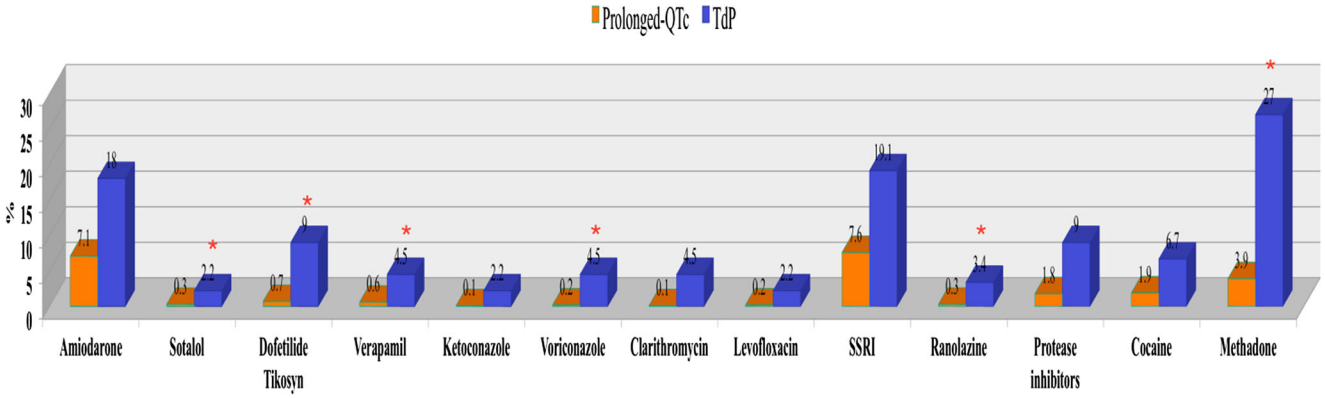

Fig. 2 Main drugs associated with causation of prolonged QTc and contribution to occurrence of torsades de pointes. Drugs with *asterisks* were statistically significant in multivariate analysis

leading to less frequent development of early after depolarizations (EAD) and homogenous ventricular dispersion in repolarization giving result to a low incidence of clinical TdP. The risk of TdP with amiodarone is thought to occur mostly in patients with other co-existing risk factors such as hypokalemia or bradycardia. Methadone was by far the leading medication implicated in the development of TdP (27 %) and an independent predictor in both univariate and multivariate analyses for the development of TdP despite the fact that it was not the most common QT-prolonging medication in our population (3.9 %). As expected, antifungal medications and class III anti-arrhythmic drugs showed the highest odd ratios in multivariate analysis for developing TdP. Nonetheless, it is important to note that these medications are generally either prescribed for short periods of time or because there is not other feasible treatment options, which in turns would dramatically affect the risk benefit ratio for use. On the contrary, most patients who use methadone remain on this therapy indefinitely, greatly prolonging time at risk. Furthermore, many of these patients have other concomitant QT-prolonging factors such as multiple QT-prolonging drugs, cocaine use, HIV infection, heart failure, and electrolyte abnormalities. These factors potentially make treated patients more vulnerable to developing TdP. It has been documented that a significant percentages of patients in methadone programs in the United States are prone to infectious diseases and psychiatric conditions, which are often treated using agents that prolong the QT (i.e., SSRI for depression, protease inhibitors for HIV infection, antipsychotics, antibiotics such macrolides and quinolones, among others). Some of these patients continue to use illicit substances (e.g., cocaine) in the context of continued or augmented methadone use. Consequently, their risk of having drug-drug interactions and TdP increases markedly [10].

Our study's univariate analysis also demonstrated an association between HIV infection and prolonged QT and TdP. In a study by Sani et al., QT prolongation was present in 28 and 45 % of patients with HIV and AIDS respectively, compared to 10 % in a non-HIV-infected cohort. This was significant even after adjustment for age, gender, and risk factors for prolonged QT including antiretroviral therapy, suggesting a risk related to HIV [11]. Although HIV has been proposed as an independent cause of prolonged QTc/TdP and our univariate analysis showed statistical significance, our multivariate analysis did not corroborate this hypothesis, probably suggesting that this patient population has increase incidence of QTc due to concomitant QTc-prolonging medications. Some studies have suggested that in these patients, the cause of TdP may be multifactorial: the virus itself, antiviral therapy, concomitant antifungal therapy, antimicrobials, psychiatric medications, and treatment for drug addictions (i.e., methadone) [12].

Based on National Survey of Substance Abuse Treatment Services (N-SSATS) from 2011, there are more than 300,000 patients in the United States enrolled in treatment centers for opioid abuse, and 85 % are on methadone [7]. Investigators analyzed the mortality associated with the use of opiates including methadone, and from 1999 to 2009, the death rate due to overdose increased fourfold. In 2009, methadone-related deaths were estimated to be 2.01/100,000 person/year [13]. Whether the deaths were solely due to respiratory depression or arrhythmias is not specified [14]. The significant rise in deaths due to methadone overdose prompted the Food and Drug Administration (FDA) to place a black-box warning in 2006 stating that these patients need frequent electrocardiographic monitoring, that methadone is relatively contraindicated in patients with QTc longer than 450 ms and that is absolutely contraindicated in patients with QTc longer than 500 ms [15]. Despite this warning, a significant number of patients on drug abuse treatment programs are still on increasing doses of methadone for a prolonged period of time without been periodically screened for QT prolongation.

The pharmacokinetics of methadone may be attributed for the unpredictable QTc prolongation and thus occurrence of TdP. Methadone has rapid oral absorption and delayed gastric

Table 2 Univariate analysis for TdP in patients with prolonged QTc

	Odds ratio	Lower	Upper	*p* value
Demographics				
Age (years)	0.992	0.978	1.005	0.227
Male	0.85	0.549	1.315	0.465
Black	0.261	0.069	0.989	0.0048
Hispanic	3.288	1.478	7.312	0.004
Other	13.422	6.305	28.573	<0.001
Electrocardiogram				
Heart rate (per minute)	0.999	0.984	1.015	0.932
QT (milliseconds)	1.009	1.007	1.012	<0.001
QTc (corrected by Bazett's formula)	1.014	1.011	1.017	<0.001
Ejection fraction (%)	0.968	0.955	0.981	<0.001
Comorbidities				
Ischemia or infarction	1.186	0.755	1.861	0.459
Stroke	1.105	0.595	2.052	0.751
Connective tissue disorder	0.377	0.052	2.741	0.335
HIV	3.301	1.66	6.563	0.001
Hypothermia	0.598	0.082	4.377	0.613
Medications				
Amiodarone	2.887	1.648	5.056	<0.001
Sotalol	6.963	1.482	32.707	0.014
Dofetilide (Tikosyn)	13.407	5.735	31.343	<0.001
Verapamil	7.524	2.479	22.839	<0.001
Ketoconazole	62.851	5.645	699.725	<0.001
Voriconazole	21.404	5.931	77.247	<0.001
Azithromycin	1.399	0.502	3.898	0.521
Clarithromycin	32.129	7.902	130.632	<0.001
Ciprofloxacin	0.778	0.282	2.148	0.628
Levofloxacin	10.456	2.081	52.544	0.004
Haloperidol	0.646	0.157	2.663	0.545
SSRI	2.884	1.668	4.984	<0.0011
Risperidone	1.511	0.36	6.345	0.573
HCTZ	0.935	0.472	1.851	0.847
Furosemide	1.416	0.918	2.182	0.116
Ranolazine	13.595	3.456	53.469	<0.001
Protease inhibitors	5.529	2.533	12.066	<0.001
Cocaine	3.804	1.588	9.114	0.003
Methadone	8.981	5.414	14.899	<0.001
Electrolytes				
Potassium (mEq/L)	0.248	0.163	0.376	<0.001
Magnesium (mg/dl)	0.377	0.194	0.733	0.004
Calcium (mg/dl)	0.982	0.774	1.246	0.881
Albumin (g/dl)	0.757	0.564	1.017	0.064
TSH	1.027	0.987	1.069	0.184
Electrolyte abnormalities				
Hypokalemia	5.003	3.187	7.853	<0.001
Hypomagnesaemia	3.962	2.127	7.382	<0.001
Hypocalcemia	1.062	0.674	1.674	0.795
hypoalbuminemia	1.255	0.787	2.002	0.34
Others				
Hypothyroidism	2.031	0.898	4.595	0.089

HIV human immunodeficiency virus, *SSRI* selective serotonin reuptake inhibitors, *HCTZ* hydrochlorothiazide, *TSH* thyroid-stimulating hormone

emptying increasing the bioavailability. It is 90 % protein bound but variation between patient populations was noted. Different factors such as drugs, malnutrition, and underlying chronic illnesses including cancer can drastically alter the concentration of free available methadone [16]. The elimination half-life of methadone is 8 to 130 h, which is longer than the analgesic action of 4–8 h. Therefore, frequent doses taken for the management of chronic pain result in accumulation of the drug [10].

Methadone- and opioid-associated mortality rates are increasing across the United States. In 2005, drug overdose

Table 3 Multivariate analysis for TdP in patients with prolonged QTc

	Adjusted odds ratio	Lower	Upper	*p* value
Black	0.217	0.040	1.182	0.077
Hispanic	3.801	1.36	10.617	0.011
Other	18.936	7.086	50.599	<0.001
Electrocardiogram				
QTc (corrected by Bazett's formula; milliseconds)	1.015	1.01	1.02	<0.001
Ejection fraction (%)	0.962	0.943	0.982	<0.001
Comorbidities				
HIV	2.254	0.354	14.373	0.390
Medications				
Amiodarone	1.659	0.702	3.923	0.249
Sotalol	12.72	1.954	82.818	0.008
Dofetilide	25.85	6.477	103.165	<0.001
Verapamil	10.984	2.683	44.968	0.001
Voriconazole	20.064	3.24	124.259	0.001
Clarithromycin	4.588	0.202	104.397	0.339
Levofloxacin	9.335	0.450	193.683	0.149
SSRI	2.562	1.1	5.967	0.029
Ranolazine	53.611	5.481	524.334	0.001
Protease inhibitors	0.593	0.068	5.156	0.636
Cocaine	1.272	0.290	5.584	0.750
Methadone	9.896	4.054	24.155	<0.001
Electrolyte abnormalities				
Hypokalemia	5.567	2.9	10.689	<0.001
Hypomagnesaemia	2.761	0.954	7.990	0.061

HIV human immunodeficiency virus, *SSRI* selective serotonin reuptake inhibitors

surpassed firearms as a cause of death. While total poisonings increased by 66 % from 1997 to 2005, methadone-related deaths increased by 468 % [6]. In West Virginia, opioids were involved in 93 % of all unintentional fatal poisonings in 2006, and methadone was found in 40 % of cases, despite being significantly less frequently prescribed than several other medications [17]. Approximately 300,000 patients receive methadone through opioid dependency programs and >700, 000 for chronic pain [7, 18]. In Utah, prescriptions for methadone increased by 727 % from 1997 to 2004. Moreover, the non-suicide methadone-related deaths rose by 1770 % in the same period [19]. While approximately ten times the number of prescriptions are written for hydrocodone and oxycodone compared to methadone, and ten times as many Americans report abusing these agents compared to methadone, the total number of deaths in 2005 was only 12 % higher for these compounds than methadone [6].

Methadone cardiotoxicity has been attributed to the blockage of the delayed rectifier potassium ion channel (IKr) and has been extensively studied [16, 20]. A study evaluated the ability of various opioid agonists, including methadone, L-acetylmethadol hydrochloride (LAAM), fentanyl, meperidine, morphine, and buprenorphine, to block the cardiac HERG K current in human cells stably transfected with the HERG potassium channel gene. Their results revealed that LAAM, methadone, fentanyl, and buprenorphine were effective inhibitors of HERG potassium current, with half maximal inhibitory concentration (IC_{50}) values in the 1 to 10 M range. The other drugs tested were far less potent with respect to HERG K current inhibition. Compared with the reported maximal plasma concentration (C_{max}) after administration of therapeutic doses of these drugs, the ratio of IC_{50}/C_{max} was the highest for codeine and morphine (455 and 400, respectively), thereby indicating that these drugs had the widest margin of safety with respect to blockade of HERG. In contrast, the lowest ratios of IC_{50}/C_{max} were observed for LAAM and methadone (2.2 and 2.7, respectively) indicating the low therapeutic window of these two medications and thus high risk of drug toxicity [21]. Interestingly, although buprenorphine blocks the HERG potassium current, this medication has a remarkable better profile in terms of $IC_{50}/C_{max,}$ which was found to be approximately 208, a hundred times safer than methadone [21].

Methadone, as a full mu opioid agonist, continues to produce effects on the receptors until either all receptors are fully activated or the maximum effect is reached. Buprenorphine, as a partial agonist, does not activate mu receptors to the same extent as methadone. Its effects increase until they reach a plateau. At that level, opioid-addicted patients can discontinue opioids use without experiencing withdrawal. Buprenorphine reaches its ceiling effect at a moderate dose, which means that its effects do not increase after that point, even with dosage incrementation.

In October 2002, the FDA approved the buprenorphine monotherapy product, Subutex, and a buprenorphine/naloxone combination product, Suboxone, for treatment of opioid addiction. Although buprenorphine is currently not recommended for the treatment of chronic or cancer pain due to its partial antagonist activity, a study in France demonstrated that it may represent a safer alternative to methadone for the treatment of narcotic addiction. In this country, buprenorphine has been widely used in the treatment of this medical condition for several years, and it was found that between 1994 and 1998, the proportion of patients whose death was classified as “treatment-related” was three times greater for patients during methadone treatment compared with those that received buprenorphine treatment [22]. Although several reports claim that methadone-related mortality is primarily due to overdose, we find it difficult to believe this theory given the fact methadone is provided to patients on a daily basis. This suggests that mortality might actually be related to arrhythmic causes.

Clinical randomized trials comparing methadone and buprenorphine have shown that both medications are equally efficacious in treating opioid dependence and in decreasing the use of illicit opioids [23, 24]. Furthermore, another randomized clinical trial demonstrated that buprenorphine was a safer option given the fact that it did not prolong the QTc interval in any of the enrolled patients in that arm (i.e., 23 vs. 0 %) [25].

Interestingly, in April 2001, the United States FDA issued a new warning about adverse cardiac events associated with the use of LAAM, an opioid agonist licensed for the treatment of narcotic addiction with almost identical chemical structure to methadone [21, 26, 27]. This warning was prompted by ten cases of serious cardiac arrhythmias reported to the FDA through their MedWatch surveillance program. A similar warning was issued by the European Agency for the Evaluation of Medicinal Products in March 2001. This agency stated that of the ten cases of serious cardiac arrhythmias reported in patients receiving LAAM, five of them were cases of cardiac arrest associated with ventricular arrhythmias. Both of these reports practically caused this medication to be removed from clinical practice [27].

Interestingly, loss of function of the HERG gene is also seen in congenital long QT syndrome type 2. To a lesser extent, other forms of congenital prolonged QT involving mutations of several genes, for example, KCNQ1 gene (type 1 long QT syndrome [LQTS]) and SCN5A gene (type 3 LQTS), may become evident when a QT-prolonging drug is used and can significantly increase the risk of TdP [28–31]. This was demonstrated by Yang et al. in a group of patients with drug-associated TdP, which revealed a 10–15 % prevalence of DNA variants in genes that code for cardiac ion channels associated with LQTS [32]. Of particular interest, almost all the drugs, that have been implicated in drug-induced QT prolongation and causing TdP, are associated with blockade of the

outward IKr by binding to the same alpha subunit, which is coded for by the HERG [33]. A link between congenital and acquired QT syndrome has been postulated given the fact that block of IKr is a known mechanism for drug-induced cardiac arrhythmias, and studies have shown that HERG associated to congenital QT II encodes IKr channels proteins providing a mechanistic link between certain forms of inherited and acquired long QT [30]. In about 5–10 % of patients, drug-induced long QT syndrome appears to represent a "forme fruste" or "subclinical" form of congenital LQTS, in which a polymorphism or mutation of one of the long QT genes remains clinically silent until the time of exposure to a drug that precipitates TdP [1]. Thus, subclinical mutations in long QT syndrome related-genes, which also have a very low penetrance, can predispose the susceptible subset of individuals to life-threatening arrhythmias during drug therapy. The clinical implications of these findings would reinforce the fact that there is a potential need to identify and screen "at risk" individuals, predominantly in those cases that involve the chronic use of QT-prolonging medications (e.g., methadone) for conditions in which even a low incidence of possibly fatal adverse events is unacceptable. It might be worth obtaining specific genetic testing for the main mutations in genes that cause congenital long QT syndrome prior to the initiation of methadone in order to risk stratify these patients [28, 34–36].

Although numerous psychiatrists and pain management providers support the concept that "methadone is a life-saving therapy" and firmly state that it would be mistake to remove it from the physician's armamentarium, this medication as well as it predecessor LAAM is associated with the potential for the most catastrophic iatrogenic complication possible such as drug-induced sudden death either due to respiratory depression or life-threatening arrhythmias. These data must make physicians aware that patients on methadone are at very high risk and that many people who die unexpectedly at home supposedly due to overdose and respiratory failure might actually have experienced TdP, but it was not documented since they are not continuously monitored.

Despite public knowledge of its pro-arrhythmic effects along with the risk of severe respiratory depression, the vast majority of patients being treated for opioid addiction are still on methadone, despite having the safer option of buprenorphine [25]. However, being a weak partial mu agonist, buprenorphine causes less analgesia and euphoria compared to methadone while still ameliorating withdrawal symptoms [25, 37]. This, along with other factors like greater costs are one of the several reasons why the adherence to therapy is low to this medication. There are actually cases in which patients undergo ICD implantation in order to continue taking methadone [38].

The truth is, buprenorphine alone has not yet been shown to prolong the QT interval and has less potential for abuse and overdose [25, 37, 39].

4.1 Limitations

This study was conducted in a retrospective fashion, and results must be received keeping in mind the limitations of such design. Bazett's formula was used to calculate the QTc interval. We are cognizant that as many as 30 % of normal ECG may be diagnosed with prolonged QT interval when this formula is used [3]. Although, the current recommendation of AHA/ACC is to implement a linear regression function (QTc=QT+ 1.75 (HR-60), we considered that this is rarely used in clinical practice [9]. Lastly, it is very difficult to draw meaningful conclusion about ranolazine and its associated risk of QTc and TdP given the small number of patients who took this medication.

5 Conclusion

Methadone is a common agent in the development of TdP in an inner city population. A more detail risk stratification and treatment options with better safety profiles should be taken into consideration when treating patients with opiate dependence and chronic pain.

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