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Review article

Methadone, QTc prolongation and torsades de pointes: Current concepts, management and a hidden twist in the tale?

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ABSTRACT

Methadone is a drug that has found widespread utility in the management of opioid addiction and pain. Along with its popularity, methadone has also earned an infamous reputation for causing prolongation of the QT interval and an increased risk of torsades de pointes.

In this article we will give a brief overview of the long QT syndromes, followed by an in-depth look at the current pathophysiologic mechanisms of methadone induced QT prolongation, a review of the existing literature and the current concepts regarding the prevention and management of methadone induced torsades de pointes. In addition, we explore the idea and implications of a genetic link between methadone induced prolongation of the QT interval and torsades de pointes.

1. Introduction

The Long QT syndrome (LQTS) is a group of heterogenous disorders characterized by lengthening of the cardiac repolarization caused by alterations in the transmembrane potassium, sodium and calcium currents. This prolongation of the cardiac action potential manifests on the electrocardiogram (ECG) as lengthening of the QT interval. The LQTS can serve as a forerunner to torsade de pointes (TdP) and sudden cardiac death.

LQTS are typically categorized as either congenital or acquired. Modern molecular techniques have enabled the identification of a subclinical or "forme fruste" of the LQTS which is characterized by the presence of an altered genotype which manifests phenotypically in the presence of triggers such as drugs or other predisposing factors.

In the United States alone, at this time there are nearly 1 million users of methadone, including patients who are being treated for opiate addiction and pain.[1] However the association of methadone with prolongation of the corrected QT interval (QTc) and the risk of a potentially fatal arrhythmia, TdP has given rise to intense scrutiny and much deliberation in the community.[2,3]

Methadone induced prolongation of QTc is viewed as an acquired trait. However the possibility of a methadone induced "forme fruste" of LQTS remains unexplored.

2. Case presentation

A 50-year-old woman with a history of Hepatitis C, acquired immunodeficiency syndrome and a history of intravenous drug use, on methadone maintenance treatment (MMT) presented with a history of recurrent episodes syncope and seizure-like activity. Results of laboratory testing on admission, including serum levels of potassium (4.1 mEq/L) and magnesium (2.2 mEq/L) were unremarkable. The ECG on admission was noted to have QTc of 657 ms (Fig. 1). A review of the patient's medication list revealed that she was on methadone 210 mg/day (recently tapered down from 360 mg/day), and highly active anti-retroviral therapy (HAART) with Ritonavir and Atazanavir. Telemetry recordings revealed that the "seizures" were associated with episodes of sustained TdP (Fig. 2) which were terminated with infusions of magnesium sulfate. A continuous lidocaine infusion was started and no recurrent episodes occurred thereafter. HAART was continued with Raltegravir. Morphine was temporarily substituted in place of methadone; the discontinuation of methadone was accompanied by normalization of the QTc within 24 h.

In light of the fact that our patient had recurrent episodes of TdP while on methadone, a decision was taken to place a dual chamber implantable cardioverter and defibrillator (ICD) prior to the

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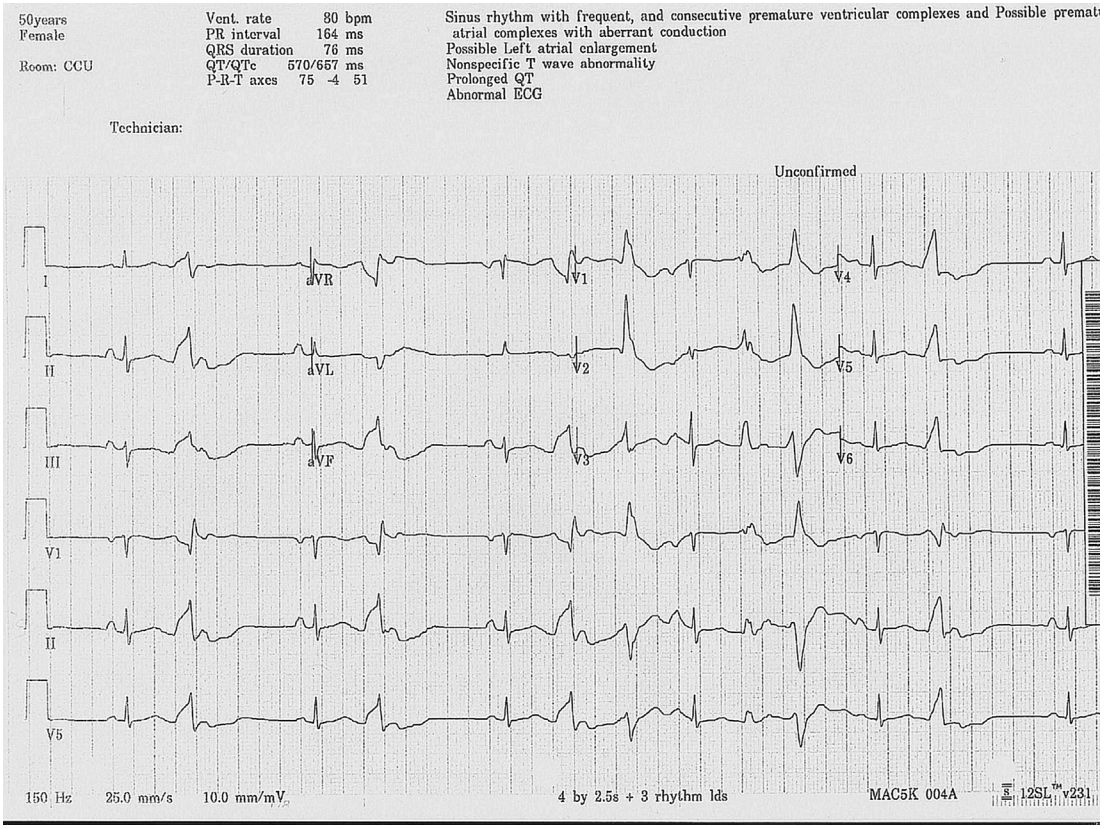

Fig. 1. 12-Lead surface electrocardiogram depicting normal sinus rhythm with polymorphic premature ventricular contractions. Also QTc is markedly prolonged (657 ms).

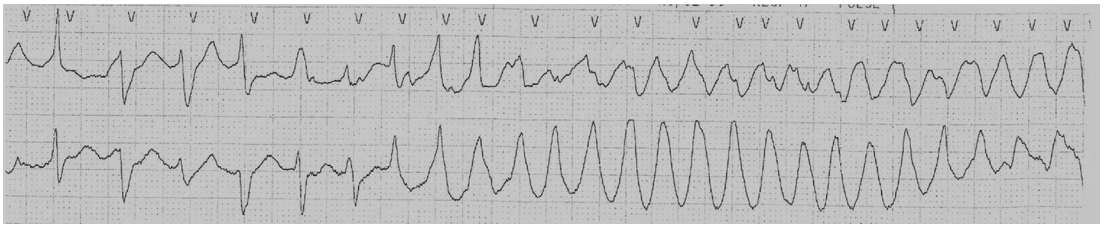

Fig. 2. Telemetry recording of an episode of torsade de pointes.

patient's return to MMT upon discharge, to protect against the future risk of a potentially fatal arrhythmic event.

3. The long QT syndromes

Syncopal events in association with quinidine therapy were first recognized in the 1920s.[4] Selzer and Wray, in 1964,[5] were the first to report prolongation of the QT interval in response to quinidine therapy. Two years later, Dessertnne[6] coined the term "Torsades de Pointes" or "twisting of the points" to describe the appearance of a ventricular tachycardia where the QRS complexes appeared to oscillate around to the isoelectric line in a sinusoidal pattern.

Congenital LQTS were first recognized in the 1950s and 1960s: The Jervell and Lange-Nielsen syndrome[7] (cardiac phenotype associated with sensorineural deafness) and the Romano-Ward variant[7] (purely cardiac). Congenital LQTS as a channelopathy, was first discovered in 1995 with the identification of mutant voltage-gated potassium and sodium channels.[8] To date, nearly a thousand different mutations in thirteen distinct genes designated as LQT1 through to LQT13 have been described. The mutations in LQT1, LQT2 and LQT3 cumulatively account for 75% of all cases of familial LQTS.[8] The other 10 minor LQTS genes make up an additional 5%; 20% of the familial LQTS cases have yet undiscovered genetic loci.[8]

The acquired forms of LQTS appear to be the result of interplay between complex cardiovascular traits, exposure to drugs and multiple environmental factors (Table 1).[2–4,8] Arguably, the most important of these is the association of LQTS with the use of numerous drugs. In fact, QT prolongation and TdP are the most common reasons for the withdrawal of drugs from markets in the U.S.[9,10]

Between the purely congenital and the drug induced forms of LQTS, lies the "forme fruste" of the congenital LQTS. This concept which was first postulated by Moss and Schwartz[11] entails that there is a subset of the population that has a genetic substrate that renders them susceptible to life threatening arrhythmias such as TdP; yet the phenotype remains clinically silent until exposure to triggers (e.g. drugs, hypokalemia etc.) which are thought to diminish the "repolarization reserve",[4,9] leading to prolongation of

Table 1
Causes of acquired LQTS.

Metabolic disorders
Electrolyte abnormalities: hypokalemia, hypomagnesemia, hypocalcemia
Starvation
Anorexia nervosa
Hypothyroidism
Cardiac disease
Bradyarrhythmias: sinus node dysfunction, AV block-second or third degree
Advanced cardiac disease
Myocardial ischemia or infarction, esp. with prominent T wave inversions
Drugs[a]
Antiarrhythmic drugs e.g.: quinidine, procainamide, sotalol
Antimicrobial drugs: erythromycin, azithromycin, levofloxacin
Antihistamines: terfenadine
HIV Protease inhibitors: ritonavir, nelfinavir, atazanavir
Psychotropic drugs: thioridazine, haloperidol, olanzapine
Motility drugs: cisapride, domperidone
Miscellaneous factors
HIV infection
Hypothermia
Connective tissue disorders with anti-Ro/SSA antibodies

[a] A comprehensive list of QT interval prolonging medications can be found at the Arizona Center for Education and Research on Therapeutics (CERT) website: http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm, www.qtdrugs.org.

the QTc and TdP. In 1997, Priori et al and Schulze et al became the first ones to separately identify two such cases of subclinical LQTS.[12] Napolitano et al[12] and Makita et al[13] subsequently identified subclinical mutations in KvLQT1 and SCN5A genes respectively. In both cases,[12,13] it was hypothesized that the mutations lead to a reduction in repolarizing currents, which remained clinically silent until exposure to cisapride. Administration of cisapride blocked the rapid delayed rectifier potassium current (Ikr) and exhausted the "repolarization reserve"[4,9] which would have otherwise compensated for the loss of function of the mutant channels, leading to prolongation of the QT interval and recurrent episodes of TdP.

3.1. Pathophysiology of LQTS

The pathophysiologic mechanisms of the congenital LQTS are outlined in Table 2.

The vast majority of drug-induced forms of LQTS are mediated through their effects on the Ikr.[9,10] The human ether-a-go-go gene (HERG or KCNH2)[14] gene encodes a potassium channel protein that regulates the Ikr.[4] The culprit drugs preferentially block the rapid component of the Ikr,[10] resulting in a delay in the Phase 3 of the ventricular or cardiac action potential. The increased duration of the action potential is manifests as QT prolongation. The prolonged repolarization can trigger early afterdepolarizations (EADs) due to activation of inward depolarizing currents, most likely L-type calcium channels or sodium–calcium exchange current.[10] The EADs can generate ectopic beats or ventricular extrasystoles if they occur in a large enough region of the heart; this "triggered activity" from EADs can serve to initiate TdP.[9,10]

Episodes of drug-induced TdP are typically preceded by a short–long–short sequence which is characterized by a premature ventricular complex (PVC), followed by a compensatory pause and then another PVC which sets off TdP.[8,9] This particular sequence is also thought to increase the transmural heterogeneity of repolarization across the myocardium.[8] Transmural dispersion (or heterogeneity) of repolarization is a physiologic phenomenon due to variations in ion channels between the different myocardial cells[9]; if exaggerated has been associated with an increased risk for TdP.[8–10]

The putative mechanism behind drug-induced TdP includes not just exposure to the drug, but also the presence of concomitant factors such as older age, hypokalemia, bradycardia, female sex etc.[2–4,8]

Clinical data[15] and in vivo evidence from Langendroff rabbit models[15–17] have established that females have a naturally longer, QTc and have a greater sensitivity to QT interval prolonging drugs. The perception that females are at a greater risk of drug-induced TdP does not stem from any single factor that is inherent to the female gender. Rather, the best evidence at this time suggests that sex hormones in males appear to attenuate drug induced QTc lengthening by regulating the QT interval.[15,16] Alterations in the expression of cardiac ion channels, regional variations in specific current densities in the myocardium have been postulated as mechanisms through which sex hormones influence cardiac repolarization, although the exact molecular mechanisms remain to be defined.[15,16]

Although it lacks specificity as predictor of the risk of TdP, QT prolongation is used as the surrogate marker for assessing the torsadogenic potential of a drug during development.[18–20] The International guidance for Clinical Evaluation of the QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (ICH E-14) states that all drugs should be subjected to a "thorough QT/QTc study" prior to registration. Although there is no consensus on the upper limit values of QT interval and changes from baseline, the guidelines suggest a sex-independent threshold for QTc prolongation of 450 ms and QTc above 500 ms as a the critical threshold value.[19]

The Arizona Center for Education & Research on Therapeutics (Arizona-CERT)[21] maintains an updated database of drugs that are

Table 2
Congenital LQTS.

	Chromosome locus	Gene symbol	Protein (symbol)	Current	Action potential
LQT1	11p15.5	KCNQ1	I_{Ks} potassium channel alpha subunit (KvLQT1)	IKs ↓	Delayed phase 3
LQT2	7q35-q36	KCNH2	I_{Kr} potassium channel alpha subunit (HERG)	IKr ↓	Delayed phase 3
LQT3	3p21	SCN5A	Cardiac sodium channel alpha subunit (Nav 1.5)	INa ↑	Prolonged phase 2
LQT4	4q25-q27	ANK2	Ankyrin B, (ANKB)	Ncx1, Na/K ATPase, InsP3[a] ↓	
LQT5	21q22.1-q22.2	KCNE1	I_{Ks} potassium channel beta subunit (MinK)	IKs ↓	Delayed phase 3
LQT6	21q22.1-q22.2	KCNE2	I_{K} potassium channel beta subunit (MiRP)	IKr ↓	Delayed phase 3
LQT7	17q23.1-q24.2	KCNJ2	I_{K1} potassium channel (Kir2.1)	IK1 ↓	Delayed phase 3
LQT8	12p13.3	CACNA1c	Voltage gated calcium channel, CaV 1.2	ICa ↑	Delayed phase 3
LQT9	3p25	CAV3	Caveolin-3	INa ↑	
LQT10	11q23	SCN4B	Cardiac sodium channel beta-4 subunit	INa ↑	Prolong the action potential
LQT11	7q21-22	Makap	A-kinase anchoring proteins	IKs ↓	
LQT12	20q11.2	SNTA1	Syntrophin	INa ↑	
LQT13	11q24.3	KCNJ5	Potassium channel Kir3.4 (GIRK4)	I_{KACh} current ↓ (inwardly rectifying potassium channel current)	Prolongs the refractory period

[a] NCx: sodium calcium exchanger; Na/K ATPase: sodium potassium ATP pump; InsP3: inositol 3-phosphate receptor.

known to prolong the QT interval and pose a risk of TdP. The list can be accessed via the internet (www.torsades.org); it includes methadone, a drug well known for its association with QT prolongation and TdP.

4. Methadone

Methadone is a long-acting synthetic opioid agonist that has a notorious reputation for causing QTc prolongation and has been associated with a high risk of TdP.[8,22,23] It was first proposed as a substitute for heroin in 1965 by Dole and Nyswander.[24] Ever since, it has emerged as a key player both in the management of opioid addiction and as an inexpensive therapy for pain. However, unexpected deaths associated with the use of methadone[24] eventually lead to a clinician safety alert from the U.S. Food and Drug Administration (FDA) in 2006, and a manufacturer's black box warning.[3,25]

4.1. Mechanism of action

Like most drugs that cause LQTS, methadone too is an inhibitor of the cardiac ion channel KCNH2[26] and causes QT prolongation in a dose dependent manner.[4,26] Increased QT dispersion (QT interval variability in electrocardiographic leads) is a marker of heterogenous cardiac repolarization and has been observed in association with methadone.[27] In addition to its effects on cardiac repolarization, methadone use is also associated with the development of bradycardia mediated via its anticholinesterase properties[28] and through its action as a calcium channel antagonist.[29]

Thus through its multiple effects of QT prolongation, increased QT dispersion and negative chronotropy, methadone poses a significant risk for the development of TdP.

4.2. Evidence

The literature on methadone-induced QT prolongation dates back to 1973 when Stimmel et al[30] reported prolongation of the QTc and electrocardiographic abnormalities in narcotic addicts that included methadone treated patients. A plethora of evidence has emerged since that time describing the nexus between QT prolongation and methadone use. A brief summary of the data from clinical case series, cross-sectional, retrospective and prospective studies is provided in Table 3.

4.2.1. Clinical case series

The published literature contains several case reports and case series linking methadone use with QTc interval prolongation and TdP.[2] The first case series from the United States was reported by Krantz et al[31] who found an association between high dose methadone use (average dose of 400 mg/day) and TdP; 12 of these 43 patients had hypokalemia or the use of another QTc prolonging medication. From1969 to 2002, 43 cases of methadone associated TdP and 16 cases of methadone induced QTc prolongation were reported to the FDA.[22] This number is likely an underestimate of the true number of cases, since less than 10% of all adverse drug reactions are estimated to be reported to the FDA MedWatch.[22] In another case series of 1800 patients, Sticherling et al[23] reported the development of near fatal TdP in five young intravenous drug abusers who were being treated chronically with methadone; concomitant use of QT prolonging agents and hypokalemia were found in four of the five cases.

4.2.2. Cross-sectional data

Evidence from five cross sectional studies[20,32–35] involving patients on oral methadone treatment showed prolongation of the QTc with a dose range of 10–1200 mg/day. One of these studies included the use of methadone for pain management and as substitution therapy[33] while the other four included patients on MMT.[20,32,34,35]

Eap et al[32] observed a dose dependent effect of methadone on the duration of the QTc interval in a cohort of 179 patients; Cruciani et al[33] and Peles et al[35] made similar observations but only in a sub group of patients. Interestingly, of the two deaths that were reported by Peles et al[35] both patients had a QTc interval that exceeded 500 ms. Maremmani et al[34] did not find any such correlation but they did note that 83% of the patients on long term MMT had a longer baseline QT interval compared with people not on long-term methadone when matched for sex and age. In the largest cross-sectional study to date, Fanoe et al[20] analyzed a cohort of 450 adult heroin addicts, of which 393 were being treated with oral methadone; the QTc interval was reported to increase by 10 ms for every 50 mg increase in the methadone dose.

4.2.3. Prospective data

Prolongation of the QTc interval has been found in five studies[27,30,36–38] of patients receiving oral methadone for either

Table 3
Description of prospective, cross-sectional, and retrospective studies that report prolongation of the QTc interval or TdP.

Study design	Indication	*N*	% N Prol	QTc; $n > 500$ ms	TdP	RF	Dose	DD	Reference
Prospective	ST	41	30	NR	No	Yes	NR	NR	Stimmel et al,[30]1973
Prospective	ST	132	NR	428; 0	No	+/−	NR	Yes	Martell et al,[36] 2003
Retrospective[a]	Pain	47	NR	NR; 0	No	No	17.8+/−20.6 mg/h	Yes	Kornick et al,[41] 2003
Retrospective	Pain	56	NR	413; 0	No	No	30 (2–480)	N/A	Reddy et al,[39] 2004
Prospective	ST	118	16	429; 0	No	+/−	80 (20–180)	No	Krantz et al,[27] 2005
Prospective	ST	167	67	431; 0	No	+/−	80 (20–180)	Yes	Martell et al,[37] 2005
Cross-sectional	Pain/ST	104	33	428; 0	No	+/−	110 (20–1200)	Yes[a]	Cruciani et al,[33] 2005
Cross-sectional	ST	83	83	423+/−40; 2	No	No	387 (10–600)	No	Maremmani et al,[34] 2005
Prospective	Pain	8	88	440; 0	No	No	57 (10–90)	No	Fredheim et al,[38]2006
Retrospective	ST	167	30	440; 27	6	+/−	100 (4–600)	Yes	Ehret et al,[40] 2006
Cross-sectional	ST	138	16	418; 3	No	+/−	171 (40–290)	Yes[b]	Peles et al,[35] 2007
Cross-sectional	ST	179	9	422; 0	No	+/−	145 (10–430)	Yes	Eap et al,[32] 2007
Cross-sectional	ST	393	32	NR; 8	No	+/−	100 (50–235)	Yes	Fanoe et al,[20] 2007
Randomized control trial	ST	53[c]	23	470[d]/490[d]; 6	No	+/−	NR (60–100)	NR	Wedam et al,[42] 2007

N = number of patients; % N Prol = percentage of patients with prolongation of the QTc interval; QTc = QT interval duration in ms; $n > 500$ ms = number of patients with QTc interval>500 ms; TdP = Torsades Pointes; RF = risk factors; Dose = dose of methadone in mg/day (range); DD = dose dependency; ST = substitution therapy; NR = not reported.

[a] Only study in the table with IV methadone.

[b] Dose dependency in a sub group of patients.

[c] Final statistical analysis included 53 patients on methadone.

[d] QTc >470 ms in males or>490 ms in females.

pain management[38] or as substitution therapy[27,30,36,37] at average doses between 30 and 180 mg/day.

Krantz et al[27] and Martell et al[37] followed new entrants into MMT programs. Both reported QTc prolongation; Krantz et al[27] also reported an increase in the QT dispersion.

4.2.4. Retrospective data

In a retrospective analysis of patients receiving oral methadone for cancer pain, Reddy et al[39] did not report QTc prolongation at low dose methadone of 30 mg. Ehret et al[40] analyzed 247 hospitalized patients with a history of intravenous drug use and found marked QTc prolongation (>500 ms) in 16% of the 167 patients on methadone therapy; six cases of TdP were also reported. QTc prolongation was not found among the intravenous drug users who were not on methadone. In addition, the study also showed that discontinuation of the methadone was associated with a shorter QTc interval. Kornick et al[41] noted a dose-dependent prolongation of the QTc with the use of intravenous methadone, but not with the use of intravenous morphine.

4.2.5. Randomized trial data

There is a relative paucity of randomized data. In a 17-week randomized study of 220 patients, who were being treated for opioid dependence with levomethadyl (75–115 mg), buprenorphine (16–32 mg), high-dose (60–100 mg) and low-dose (20 mg) methadone, Wedam et al[42] found a prolongation of the QTc interval in 23% of the patients who received methadone and had a normal QTc interval at baseline. In addition, 10% of the methadone treated group had a QTc interval of more than 500msec at some point over the 16-week study period.

4.3. Predisposing factors

Prolongation of the QTc is accepted as risk factor for the development of TdP[2] but as is the case with other QTc prolonging drugs, methadone's ability to trigger TdP is thought to be modulated by the presence of several factors.

Methadone prolongs QTc in a dose dependent manner.[37,43] Drugs that increase the plasma concentrations of methadone (e.g. CYP3A4 system inhibitors such as ritonavir, erythromycin etc.)[10] have been identified as risk factors, although their precise role remains unclear at this time.[8] Other factors that predispose to a methadone induced TdP include hypokalemia,[3,8] hypomagnesemia[3,8] and hypocalcemia[8] and female sex.[3] However, there is evidence in the existing literature that methadone even in absence of other risk factors is sufficient to cause QTc prolongation and TdP.[38,44]

4.4. "Subclinical LQTS" and methadone

In spite of the compelling body of evidence linking the use of methadone to prolongation of the QTc interval and development of TdP, the question as to why methadone is not equipotent in triggering TdP across the entire at-risk population of methadone users remains unanswered. As mentioned earlier in this review, one possibility that remains unexplored is a methadone-induced TdP may represent a "*forme fruste*" of congenital LQTS.

Genetic susceptibility to drug induced cardiac arrhythmias, whether due to LQTS causing mutations or the presence of functional single nucleotide polymorphisms is now an irrefutable fact. It merits consideration in cases of drug-induced LQTS and TdP, particularly with regard to high risk drugs such as anti-arrhythmic drugs and methadone.[8] The works of Priori et al,[12] Schulze et al[12] and Makita et al[13] raise the possibility that not all the cases of drug-induced arrhythmias occur in a sporadic and unpredictable manner; that in fact there may be individuals who are predisposed to developing potentially life-threatening arrhythmias and may stand to benefit if they can be identified. Clinical studies of congenital LQTS have shown evidence of incomplete penetrance, as low as 25%,[45] which implies that family members of patients afflicted with LQTS who are considered to be "normal" i.e. without phenotypical evidence of prolonged QT may still be silent gene carriers who are at risk of developing TdP if exposed to offenders. Thus the cumulative population that stands to be affected by a given drug extends not only to these "silent carriers", but can also afflict 50% of their offspring as the genes are transmitted in an autosomal dominant fashion.

If the concept of a "*forme fruste*" of familial LQTS is extrapolated to methadone, the hypothesis can portend far reaching clinical consequences. The yield from genetic testing of the three major LQTS susceptibility genes i.e. LQT1, LQT2 and LQT3 is approximately 10%–15% in cases of isolated drug-induced acquired LQTS.[46–48] Polymorphisms affecting cardiac channel genes (e.g. LQT3-like syndrome resulting from polymorphism affecting SCN5A-S1103Y) which contribute to a reduced repolarization reserve and hence increased susceptibility to arrhythmias[8,10] have also been identified.[8] Case series of drug-induced TdP have implicated subclinical congenital LQTS in 5%–20% of cases.[46–48] If these results are projected on to the nearly 250,000 patients in opioid treatment programs[1] and the nearly 720,000 patients receiving methadone for chronic pain syndromes throughout the United States,[1] the consequences can be momentous; this excludes the potential at-risk population that may result from the autosomal dominant transmission of this genetic trait. Not only would such a relationship call for a need to identify and screen "at risk" individuals and families, but would also call for greater vigilance in monitoring for development of TdP.

Methadone continues to play a pivotal role in the treatment of opioid addiction and pain management. MMT programs have been hugely successful in reducing rates of addiction related crimes, reduction in the transmission of diseases including human immunodeficiency virus.[44] Methadone has also been shown to reduce mortality among intravenous drug users and treated versus untreated heroin addicts.[1,10] Thus the pharmaco epidemiologic implications of finding a genetic culprit for at least a proportion of methadone drug users who develop TdP are potentially staggering. The problem is compounded by the fact that methadone is a medication with few therapeutic alternatives. Buprenorphine is an FDA approved medication for patients on methadone who develop marked QTc prolongation or TdP[1]; it has not been associated with TdP.[27,42] However, data from randomized control trails indicates that buprenorphine has lower retention rates than methadone, thus necessitating the continuation of methadone in dependent patients.[44]

4.5. Management

The management of methadone-induced prolongation of the QTc and TdP revolves around diligent monitoring to reduce the risk of TdP and the management of TdP, should it occur.

In view of the significant risk of TdP to methadone users, an expert panel was convened, which issued a set of guidelines[1] that is applicable to all patients either currently under treatment with methadone or being considered for the initiation of methadone treatment for addiction or pain, the only exception being patients with terminal, intractable cancer pain. To reduce the risk of TdP, the guidelines state the following: 1) notifying patients of arrhythmia risk when prescribing methadone, 2) inquiring about history of arrhythmia, syncope, and structural heart disease, 3) obtaining a pre-treatment ECG to measure the QTc interval and follow-up ECGs within 30 days and annually, and 4) evaluating additional ECGs if

methadone dose exceeds 100 mg/day or if syncope or seizures occur. If the QTc interval is greater than 450 ms but less than 500 ms, review risks/benefits and monitor closely. If the QTc interval exceeds 500 ms, consider discontinuing methadone, reducing the dose and/or eliminating modifiable risk factors.

The 2006 American College of Cardiology/American Heart Association/European Society of Cardiology guidelines for the management of patients with ventricular arrhythmias[49] recommend that in hemodynamically unstable patients, and in those cases where TdP does not terminate spontaneously, immediate direct current cardioversion should be performed. In addition to discontinuing offending agents and correction of electrolyte abnormalities, intravenous magnesium sulfate can be infused as a first line agent regardless of the serum levels. Temporary or long term pacing can also be considered to prevent bradycardia and long pauses that may trigger TdP. Other interventions that can be considered include: Isoproterenol as a temporary alternative in cases of recurrent TdP in patients who do not have congenital LQTS, potassium repletion and the use of intravenous lidocaine or oral mexiletine in patients with LQT3 and TdP.

The evidence for use of ICDs in patients with methadone-induced recurrent TdP is limited[23,31,44] and thus has not been included in the current guidelines as a standard of care, although it can serve as a potentially lifesaving device in patients with recurrent arrhythmias.

Our patient, for all practical purposes, presented a case of acquired QT prolongation secondary to methadone use. Given the clinical implications and risks associated with placement of an ICD, the prudent next step would have been to place the patient on a trial of buprenorphine, as a substitute for methadone. However, the management of our patient posed a dilemma for several reasons: our patient had a long standing history of being on MMT (>7 years), and was not agreeable to using buprenorphine instead of methadone. Given the likelihood of non-compliance in this case, coupled with the fact that buprenorphine has low retention rates in methadone dependent patients, the decision to place an ICD, albeit perhaps a bit hastily, was undertaken.

Our patient had multiple risk factors for methadone-induced TdP: female sex; exposure to QT prolonging drugs, Atazanavir and Ritonavir.[21] Ritonavir is also a CY3A4 inhibitor.[40] Genetic testing in this case of methadone-induced QTc prolongation and TdP, unfortunately could not be undertaken as informed consent could not be obtained from the patient.

5. Conclusions

The evolution of elegant molecular studies, together with the identification of environmental stressors has now raised the possibility of a new paradigm in drug-induced LQTS; a common model in which the genetic factors alter the manifestation of clinical phenotypes. The possibility that methadone-induced TdP may represent a "*forme fruste*" of LQTS remains uncharted. Should such an association be discovered, it would have far reaching pharmacoeconomic implications, both in terms of ensuring the availability of drugs for the population that requires them, but making certain the avoidance of their use in genetically predisposed individuals in whom potentially life-threatening effects may occur.

Conflicts of interest

All authors have none to declare.

References

1. Krantz MJ, Martin J, Stimmel B, Mehta D, Haigney MC. QTc interval screening in methadone treatment. *Ann Intern Med*. 2009;150:387–395.
2. Cruciani RA. Methadone: to ECG or not to ECG that is still the question. *J Pain Symptom Manage*. 2008;36:545.
3. Modesto-Lowe V. Methadone deaths: risk factors in pain and addicted populations. *J Gen Intern Med JGIM*. 2010;25:305–309.
4. Wood AJ, Roden DM. Drug-induced prolongation of the QT interval. *N Engl J Med*. 2004;350:1013–1022.
5. Selzer A, Wray HW. Quinidine syncope: paroxysmal ventricular fibrillation occurring during treatment of chronic atrial arrhythmias. *Circulation*. 1964;30:17–26.
6. Dessertenne F. La tachycardie ventriculaire a deux foyers opposes variables. *Arch Mal Coeur*. 1966;59:263–272.
7. Chiang CE, Roden DM. The long QT syndromes: genetic basis and clinical implications. *J Am Coll Cardiol*. 2000 Jul;36:1–12.
8. Drew BJ, Ackerman MJ, Funk M, et al. Prevention of torsade de pointes in hospital Settings: a scientific statement from the american heart association and the american college of cardiology foundation endorsed by the american association of critical-care nurses and the international society for computerized electrocardiology. *J Am Coll Cardiol*. 2010;55:934–947.
9. Kannankeril PJ, Roden DM. Drug-induced long QT and torsade de pointes: recent advances. *Curr Opin Cardiol*. 2007;22:39.
10. Gupta A, Lawrence AT, Krishnan K, Kavinsky CJ, Trohman RG. Current concepts in the mechanisms and management of drug-induced QT prolongation and torsade de pointes. *Am Heart J*. 2007;153:891–899.
11. Moss AJ, Schwartz PJ. Delayed repolarization (QT or QTU prolongation) and malignant ventricular arrhythmias. *Mod Concepts Cardiovasc Dis*. 1982 Mar;51:85–90.
12. Napolitano C, Schwartz PJ, Brown AM, et al. Evidence for a cardiac ion channel mutation underlying Drug-Induced QT prolongation and Life-Threatening arrhythmias. *J Cardiovasc Electrophysiol*. 2007;11:691–696.
13. Makita N, Horie M, Nakamura T, et al. Drug-induced long-QT syndrome associated with a subclinical SCN5A mutation. *Circulation*. 2002;106:1269–1274.
14. Newton-Cheh C, Guo CY, Larson MG, et al. Common genetic variation in KCNH2 is associated with QT interval duration the Framingham heart study. *Circulation*. 2007;116:1128–1136.
15. EBERT SN, LIU X, WOOSLEY RL. Female gender as a risk factor for drug-induced cardiac arrhythmias: evaluation of clinical and experimental evidence. *J Women's Health*. 1998;7:547–557.
16. Drici MD, Burklow TR, Haridasse V, Glazer RI, Woosley RL. Sex hormones prolong the QT interval and downregulate potassium channel expression in the rabbit heart. *Circulation*. 1996;94:1471–1474.
17. Liu X, Katchman A, Drici M, et al. Gender difference in the cycle length-dependent QT and potassium currents in rabbits. *J Pharmacol Exp Ther*. 1998;285:672–679.
18. Redfern W, Carlsson L, Davis A, et al. Relationships between preclinical cardiac electrophysiology, clinical QT interval prolongation and torsade de pointes for a broad range of drugs: evidence for a provisional safety margin in drug development. *Cardiovasc Res*. 2003;58:32–45.
19. Food U. Drug administration: guidance for industry: E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. *Cent Drug Eval Res*. 2005.
20. Fanoe S, Hvidt C, Ege P, Jensen GB. Syncope and QT prolongation among patients treated with methadone for heroin dependence in the city of copenhagen. *Heart*. 2007;93:1051–1055.
21. Arizona C. *QT Drug lists*. Tucson, AZ: The University of Arizona Center for Education and Research on Therapeutics, Arizona Health Sciences Center; 2013.
22. Pearson EC, Woosley RL. QT prolongation and torsades de pointes among methadone users: reports to the FDA spontaneous reporting system. *Pharmacoepidemiol Drug Saf*. 2005;14:747–753.
23. Sticherling C, Schaer BA, Ammann P, Maeder M, Osswald S. Methadone-induced torsade de pointes tachycardias. *Swiss Med Wkly*. 2005;135:282–285.
24. Ferrari A, Coccia CPR, Bertolini A, Sternieri E. Methadone—metabolism, pharmacokinetics and interactions. *Pharmacol Res*. 2004;50:551–559.
25. Matlock A. A continuing black hole? The FDA boxed warning: an appeal to improve its clinical utility. *Clin Toxicol*. 2011;49:443–447.
26. Katchman AN, McGroary KA, Kilborn MJ, et al. Influence of opioid agonists on cardiac Human ether-a-go-go-related gene K currents. *J Pharmacol Exp Ther*. 2002;303:688–694.
27. Krantz MJ, Lowery CM, Martell BA, Gourevitch MN, Arnsten JH. Effects of methadone on QT-Interval dispersion. *Pharmacother J Hum Pharmacol Drug Ther*. 2005;25:1523–1529.
28. Eikenburg D, Stickney J. Anti-cholinesterase activity of 1-α-acetylmethadol: relationship to bradycardia. *Gen Pharmacol Vasc Syst*. 1979;10:195–200.
29. Seyler DE, Borowitz JL, Maickel RP. Calcium channel blockade by certain opioids. *Fundam Appl Toxicol*. 1983;3:536–542.
30. Stimmel B, Lipski J, Swartz M, Donoso E. Electrocardiographic changes in heroins, methadone and multiple drug abuse: a postulated mechanism of sudden death in narcotic addicts. *Proc Natl Conf Methadone Treat*. 1973;1:706–710.
31. Krantz MJ, Lewkowiez L, Hays H, Woodroffe MA, Robertson AD, Mehler PS. Torsade de pointes associated with very-high-dose methadone. *Ann Intern Med*. 2002;137:501–504.
32. Eap CB, Crettol S, Rougier J, et al. Stereoselective block of hERG channel by (S)-methadone and QT interval prolongation in CYP2B6 slow metabolizers. *Clin Pharmacol Ther*. 2007;81:719–728.
33. Cruciani RA, Sekine R, Homel P, et al. Measurement of QTc in patients receiving chronic methadone therapy. *J Pain Symptom Manage*. 2005;29:385–391.

34. Maremmani I, Pacini M, Cesaroni C, Lovrecic M, Perugi G, Tagliamonte A. QTc interval prolongation in patients on long-term methadone maintenance therapy. *Eur Addict Res*. 2004;11:44–49.
35. Peles E, Bodner G, Kreek MJ, Rados V, Adelson M. Corrected-QT intervals as related to methadone dose and serum level in methadone maintenance treatment (MMT) patients—a cross-sectional study. *Addiction*. 2007;102:289–300.
36. Martell BA, Arnsten JH, Ray B, Gourevitch MN. The impact of methadone induction on cardiac conduction in opiate users. *Ann Intern Med*. 2003 Jul 15;139:154–155.
37. Martell BA, Arnsten JH, Krantz MJ, Gourevitch MN. Impact of methadone treatment on cardiac repolarization and conduction in opioid users. *Am J Cardiol*. 2005;95:915–918.
38. Fredheim OMS, Borchgrevink PC, Hegrenæs L, Kaasa S, Dale O, Klepstad P. Opioid switching from morphine to methadone causes a minor but not clinically significant increase in QTc time: a prospective 9-month follow-up study. *J Pain Symptom Manage*. 2006;32:180–185.
39. Reddy S, Fisch M, Bruera E. Oral methadone for cancer pain: no indication of QT interval prolongation or torsades de pointes. *J Pain Symptom Manage*. 2004;28:301.
40. Ehret GB, Voide C, Gex-Fabry M, et al. Drug-induced long QT syndrome in injection drug users receiving methadone: high frequency in hospitalized patients and risk factors. *Arch Intern Med*. 2006;166:1280.
41. Kornick CA, Kilborn MJ, Santiago-Palma J, et al. QTc interval prolongation associated with intravenous methadone. *Pain*. 2003;105:499–506.
42. Wedam EF, Bigelow GE, Johnson RE, Nuzzo PA, Haigney MC. QT-interval effects of methadone, levomethadyl, and buprenorphine in a randomized trial. *Arch Intern Med*. 2007;167:2469.
43. Krantz MJ, Kutinsky IB, Robertson AD, Mehler PS. Dose-Related effects of methadone on QT prolongation in a series of patients with torsade de pointes. *Pharmacother J Hum Pharmacol Drug Ther*. 2003;23:802–805.
44. Patel AM, Singh JP, Ruskin JN. Role of implantable cardioverter-defibrillators in patients with methadone-induced long QT syndrome. *Am J Cardiol*. 2008;101:209–211.
45. Priori SG, Napolitano C, Schwartz PJ. Low penetrance in the long-QT syndrome: clinical impact. *Circulation*. 1999;99:529–533.
46. Yang P, Kanki H, Drolet B, et al. Allelic variants in long-QT disease genes in patients with drug-associated torsades de pointes. *Circulation*. 2002;105:1943–1948.
47. Lehtonen A. Further evidence of inherited long QT syndrome gene mutations in antiarrhythmic drug-associated torsades de pointes. *Heart Rhythm*. 2007;4:603–607.
48. Paulussen AD, Gilissen RA, Armstrong M, et al. Genetic variations of KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2 in drug-induced long QT syndrome patients. *J Mol Med*. 2004;82:182–188.
49. Zipes DP, Camm AJ, Borggrefe M, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. A report of the American College Of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for practice guidelines (writing committee to develop guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death). *J Am Coll Cardiol*. 2006;48:e247–e346.

Abbreviations:

QTc: corrected QT interval
TdP: torsades de pointes
MMT: methadone maintenance treatment
ms: milliseconds
ECG: electrocardiogram
LQTS: Long QT syndrome
FDA: U.S. Food and Drug Administration
EAD: early afterdepolarization
PVC: premature ventricular complex