

Methadone's Role in Torsade de Pointes Questioned

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Evidence-Based Imperative

The first published multicase report of torsade de pointes (TdP) in patients taking oral methadone recently appeared in the *Annals of Internal Medicine (AIM)*, September 17, 2002.[1] Additionally, a single-case abstract was published in Switzerland last spring.[2] These important case reports are worthy of notice and closer inspection.

TdP is a serious clinico-electrocardiographic syndrome characterized by an abnormally prolonged QT interval (or, QTc, corrected for heartbeat) and the occurrence of potentially life-threatening ventricular tachyarrhythmias. Two major causes have been distinguished: *congenital* long QT syndrome (LQTS), an inherited myocardial ion channel pathology, and; *acquired* LQTS, which is often drug-induced but is still under investigation to define underlying mechanisms.[3]

Discussions of these topics have been previously provided in various *A.T. Forum* publications.[4-7] These are referenced in this "Update" report and also may be accessed for download at www.atforum.com.

It must be acknowledged that anecdotal cases are the weakest form of scientific evidence, and the case presentations in the *AIM* article and Swiss abstract leave many questions unanswered. In particular, is methadone the culpable agent, a minor contributor to TdP, or completely benign?

Considering methadone's more than 35-year history of safe use in millions of persons worldwide, it seems reasonable to consider that other factors might have played more crucial roles. Krantz and coauthors recommended in the *AIM* article that their cases "should not be interpreted to suggest that high-dose methadone cannot be used safely." However, at the same time they concluded, "this case series raises concern that very-high-dose methadone may be associated with torsade de pointes." [1]

In view of these inferences, it is imperative to examine the cases from a critical perspective with an emphasis on available scientific evidence.

U.S. MMT Cases

Krantz et al. described 17 patients taking oral methadone who experienced TdP. This was based on information gathered retrospectively, spanning 1996 to 2001, from methadone maintenance treatment (MMT) programs in the United States (9 patients) and a pain management center in Canada (8 patients).[1] The researchers reviewed patient charts to assess QTc intervals and identify associated risk factors for arrhythmia, which were found in 14 patients. Average methadone dose in the 17 patients was 397 (\pm 283) mg/day and the mean QTc interval was 615 (\pm 77) msec. (QTc >500 msec has been associated with an increased risk of TDP [8]). All 17 patients survived, although 14 required a cardiac defibrillator or pacemaker.

The authors specified that daily methadone doses >60 mg were "high dose," but this is uncorroborated. Initial research by Dole and colleagues found that 80 to 120 mg/d was most effective,[9] and 60 mg/d was the *minimum* level later recommended by national consensus panels.[10] The latest national survey of MMT programs in America found that nearly two-thirds of patients were receiving >60 mg/d and almost a third received >80 mg/d.[11] Furthermore, due to individual variability in methadone metabolism, research has demonstrated that doses 100 mg/d and much higher are optimal for large proportions of patients.[12,13] Therefore, designations of "high" or "very high" dose are arbitrary, and more reflective of a particular bias or treatment philosophy than available evidence.

The Krantz et al. cases actually portray two distinct subgroups of patients. According to Krantz, the first 9 patients listed in a table accompanying the *AIM* article were from MMT programs (personal communication 8/29/02), although this was not mentioned in the article. These are shown in **Table 1**.

Methadone dosing in the pain patients was significantly higher than in the MMT subgroup (mean 541.25 \pm 156 vs 269 \pm 316 mg/d, respectively; $p = 0.04$). Other factors also would likely be different in the pain patients: illicit drug use history, current physical status, and concomitant therapies for pathology causing pain.[1] There have been case

Table 1: Characteristics of 9 MMT Patients with TdP[1]

Pt #	Sex	Age (yrs)	Dose (mg/d)	Tx Dur. (mo)	QTc (msec)	Contrib. Drug(s)	Potassium (mmol/L)	Structural Heart Dis.
1†	M	50	1000	>12	600	olanzapine	4.1	No
2†	M	52	550	9	625	none	4.6	No
3	M	60	97	>12	560	none	4.3	No
4	F	51	90	4	585	cocaine	(3.2)*	Yes
5†	F	45	85	3	590	alcohol	4.1	No
6	F	46	126	6	500	alcohol, fluoxetine	(2.3)*	No
7	M	38	300	>12	700	LAAM, fluoxetine	4.0	No
8	M	51	110	>12	570	nefinavir	4.1	No
9	F	47	65	2	540	olanzapine, alcohol	(3.0)*	No

* Serum potassium below reference range of 3.5 mmol/L.

† Patients with methadone dose increase within 1 month of arrhythmia.

reports of cardiac conduction disturbances in pain patients administered high-volume intravenous methadone, but the solution contained an implicated cardiotoxic preservative, chlorobutanol.[14] Therefore, methadone in pain patients should be investigated separately.

Methadone doses in most of the 9 MMT patients were at modest levels, although 3 patients – at 1000, 550, 300 mg/d – distorted the subgroup mean. Five patients were receiving \leq 110 mg/d, which should be considered within a typical range.[1] Therefore, “very-high-dose” is not an issue and other factors might be of more importance.

The authors note that there were known risk factors for arrhythmia in all but 2 of the patients (#2 and #3).[1] However, according to Krantz (personal communication 8/28/02), patient #2 at 550 mg/d was known to take extra doses of methadone on his own (amount unknown), and patient #3 had ongoing bradycardia of undetermined etiology for some time prior to the TdP event.

Other information was lacking in the *AIM* article, although it could be important for critical interpretation of the cases. For example, nothing is mentioned regarding patients’ drug-abuse histories, physical status, lifestyle factors, or alternative medicine use. Preexisting cardiac conduction disturbances or possible genetic predispositions to such disorders are not addressed, and methadone serum levels were not measured even during the cardiac crises.

Swiss Case

There was a previously published single-case report of TdP in an MMT patient by Bittar et al. in Switzerland: see **Table 2**.^[2] This exemplifies the many confounding risk factors that may be encountered in a patient receiving an optimal daily dose of methadone and apparently thriving with a relatively prolonged QTc interval of 480 msec, possibly related to physical illness (HIV, HCV, seizure disorder), ongoing substance abuse, and/or genetic influences. The patient became destabilized with the introduction of antiretroviral medications; although, only one (zidovudine) was a P450 enzyme substrate and none of them have been reported to be proarrhythmic,[15] so drug-drug interactions were unlikely. Methadone was an imputed agent, but its exact role and why this patient suddenly became sensitized to it after 7 years of safe use are undetermined. This patient might have represented a rare, idiopathic case.

Background Prevalence

According to current estimates nearly 61 million Americans have cardiovascular disease, including coronary artery disease (CAD), which is the number one cause of death in the Western world.[16] There are an estimated 300,000 to 400,000 sudden cardiac deaths each year in the U.S., with most due to ventricular arrhythmias. An investigation at one institution found the prevalence of LQTS of unknown origin was 7% among more than

34,000 patients undergoing routine ECGs during a six month period.[4,16,17]

MMT patients are part of this larger demographic, although their risks may be amplified by former and current illicit-drug and alcohol abuse. Furthermore, a high percentage of opioid-addicted persons have cardiac abnormalities, including: cardiomegaly, infectious endocarditis, coronary artery abnormalities, acquired valvular disease, primary or secondary myocardial heart disease, pulmonary-associated heart disease, and congenital cardiac anomalies.[18] Illicit-drug users and alcoholics also expose themselves to a number of general health risks and infectious diseases, and are less likely to regularly interface with the healthcare system.[7]

A genetic predilection for LQTS has been proposed to exist in approximately 1 in 7000 individuals, or roughly 50,000 persons in the U.S. and more than 200,000 persons worldwide.[4,17] Some patients with apparent drug-induced LQTS may, in fact, have an underlying genetic predisposition. The percentage of patients harboring silent, asymptomatic genetic abnormalities of ion channel structure, and potentially prone to developing TdP with drugs well-tolerated by most persons, may be larger than is commonly assumed. [17,19]

There are approximately 180,000 persons in U.S. MMT programs at any one time,[6] although the annual number of participants would be much higher due to turnover. Using figures above, LQTS might be normally expected in a *minimum* of 8960 patients (7%), with an unknown portion having genetic predispositions. Data are unavailable to calculate numbers likely progressing to TdP, but even a small percentage would be noteworthy.

The Krantz et al. cases, collected during a 6-year period, may represent an epidemiologically expected prevalence of prolonged QTc and TdP in their MMT population. However, patient census data, including how many were at “very-high-dose” methadone, are not

reported to calculate even a crude incidence rate, and the authors concede “we cannot estimate the actual incidence of torsade de pointes in methadone-treated patients.”[1]

A.T. Forum examined all adverse event (AE) reports regarding oral methadone used in treating opioid dependence submitted to the U.S. FDA from November 1997 to November 2000.[6] Of 170 AEs reported during that 3-year period, only 6 (4%) were cardiac related, including 1 case each of LQTS and TdP. Presently designed AE-gathering systems are voluntary and inadequate, and some have contended that only 1% of adverse reactions to any drug are reported to the FDA.[15] However, even 100 cases of LQTS during a 3-year time frame in the entire MMT population, and likely much fewer cases of TdP, could be within an expected, naturally-occurring incidence rate.

Table 2: TdP in Swiss MMT Patient^[2]

Male, age 39, in MMT for 7 years (115 mg/d methadone), during which time he was heroin-free. He had not taken cocaine in the past year, but current drug use included a benzodiazepine (oxazepam), alcohol, and marijuana. He was HIV and chronic-HCV positive, and had been taking valproic acid for seizures since childhood. Baseline QTc was 480 msec. Cardiac history of the patient and his family was not reported.

A few days after initiating triple-drug antiretroviral therapy – abacavir, lamivudine, zidovudine – the patient developed epigastralgia and vomiting for 2 days. He came to the hospital emergency room in opioid withdrawal, evidenced by a subtherapeutic methadone serum level. Electrolytes were normal.

The patient developed bigeminy and bradycardia 15 minutes after administration of normal daily methadone dose per rectum; QTc was 480 msec. Ventricular tachycardia appeared, followed by ventricular fibrillation and TdP. The patient was resuscitated and methadone was replaced by oral morphine solution.

In the following days, QTc shortened to 430 msec, and a metabolic disorder, myocardial ischemia, or valve prolapse were ruled out. A methadone rechallenge at 40 mg/d was initiated under medical supervision and after a few days the QTc lengthened to 520 msec. Methadone was stopped and the patient was discharged from the hospital on slow-release morphine. Two weeks later, the QTc returned to 480 msec.

A.T. Forum also conducted an informal survey of 6 leading MMT practitioners, representing 117 years of collective experience in treating more than 29,000 methadone-maintained patients.[5] In addition to noting that they had not observed a single heart problem that they would attribute directly to methadone, there appeared to be a lower prevalence of CAD than might be expected in this population. While this survey was subject to recall bias and other shortcomings, it does imply that the relatively low proportion of cardiac-related AEs reported to the FDA may have been valid.

Confounding Factors

Krantz and colleagues, concede that most cases of drug-induced TdP involve “a confluence of factors.”[1] Separating the putative influence of methadone from confounding factors can be problematic.

There are more than 65 common prescription drugs [15] and 40 physical conditions [4,17] known to potentially prolong the QT interval and influence TdP. Among the many physical conditions are metabolite disturbances, evident in 3 of the *AIM* cases,[1] and HIV and liver disease mentioned in the Swiss report.[2] Women typically have longer QTc intervals than men and are at greater risk for cardiac electrical-conduction disturbances.[4,17]

Patients in MMT have additional risks due to past or present use of addictive substances with demonstrated cardiotoxicity, including: heroin, cocaine, alcohol, marijuana, and tobacco. Plus, during MMT, patients are frequently prescribed one or more psychotropic medications that may alter cardiac electrical conduction.[4,8,15,20]

Laboratory Evidence

Laboratory experiments have demonstrated methadone effects on electrical conduction in various cell types. In sheep heart cells, methadone at high concentrations delayed electrical conduction. In squid and chick cells, methadone slowed potassium and, to a lesser degree, sodium and calcium electrical currents across cell membranes. This effect also was demonstrated by reduced swimming speed in protozoa, and the slowing was more than doubled by the addition of alcohol.[4]

In guinea-pig and cat myocardium, methadone strengthened contractile force (inotropic effect); however, at doses 10 times peak toxic concentration in humans methadone produced a negative inotropic effect. This also was observed in rat tissues and appeared related to methadone’s ability to retard inward calcium currents.[4]

Most recently, it was reported that methadone diminished potassium ion flow and reduced repolarization currents by half their maximal strength in transfected human embryonic kidney (HEK) cell cultures. [21] However, the clinical significance of this is undetermined and the effect was seen at methadone concentrations nearly 9 times greater than usual therapeutic serum levels in MMT patients.

While laboratory research implies that methadone may influence cardiac electrical conduction across certain ion channels, and in a dose-dependent fashion, those effects have not been demonstrated as clinically harmful in humans. Some of methadone’s actions may actually provide a degree of cardiac protection in certain MMT patients, although this still needs clinical verification.

As noted, methadone appears to reduce calcium flow into cardiac tissues, and it has been proposed that decreases in intracellular calcium may protect the heart from calcium overload during stress reactions. Furthermore, research in rats demonstrated

that cocaine-related myocardial infarction could be prevented by blocking calcium channels, and experiments in mice found that opioids helped protect the heart from adverse cocaine effects.[4]

In an article for *A.T. Forum* Krantz himself noted, “Calcium channel-blocking medications lead to slower heart rates and reduced cardiac work, and these agents are effectively used to treat CAD patients who develop symptoms of angina. Also, opiates, including methadone, are known to reduce blood pressure and slow the heart rate. Thus, due to these properties, methadone is theoretically protective in preventing or reducing cardiac ischemia.”[7]

Clinical Evidence

A study by Stimmel and colleagues in 1973 [22] was an early demonstration that asymptomatic multidrug abusers with recent heroin use exhibit abnormal ECGs, including QTc prolongation in 31%. Overall, 61% (33/54) of drug-dependent persons studied were found to have ECG alterations.

Among 41 patients attending an MMT program, but continuing multidrug and alcohol abuse, 66% had ECG alterations early in the program, primarily QTc prolongations of undefined length in 34% and bradyarrhythmias in 31%, which were possibly preexisting conditions. Notably, after 4 or more months in MMT, and abstinence from all illicit drugs and alcohol, the QTc irregularities vanished in 54% of those patients retested. Whereas, 4 patients who continued sporadic illicit-drug and alcohol abuse while in MMT developed *de novo* QTc prolongation.[22] Thus, ***in the absence of confounding substance abuse, methadone may have an essentially neutral or possibly stabilizing effect on QTc.***

Mathot and colleagues, working in a Belgium psychiatric clinic, reported on 78 MMT patients who exhibited QTc intervals 1.4% longer than 128 psychiatric patients not administered methadone (mean 446 vs 440 msec, respectively; $p = 0.07$).[20] This small difference was not statistically significant and it is important to note that all of the MMT patients were concurrently prescribed one (22.3%) or more (77.6%) psychotropic agents (including olanzapine and fluoxetine as in the Krantz et al. cases [1]). Nearly one-fifth of all patients with prolonged QTc intervals also continued alcohol abuse.

As evidence of methadone’s QTc-prolonging propensities, and in corroboration of laboratory findings,[21] Krantz et al. [1] called attention to a study by Huber and colleagues [23] as “demonstrating an 8% absolute increase in the QTc after methadone initiation.” However, this was a multifaceted investigation with several confounding elements.

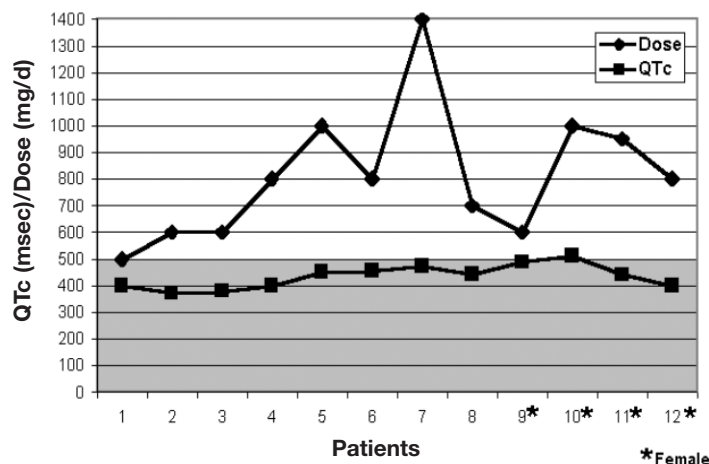
The primary objective of the study was to evaluate the extent and clinical significance of QTc interval prolongation in subjects receiving a 30-day methadone regimen followed by transition to LAAM therapy. At baseline 91% of subjects had normal QTc intervals (≤ 430 msec men; ≤ 450 msec women) and, in an intention-to-treat analysis, 90 patients completed the MMT arm.[23]

Although there was a statistically significant increase in the overall mean QTc from baseline to the end of the methadone phase, only 4 subjects (5%) were classified as having prolonged QTc intervals (>450 msec men; >470 msec women), while most subjects (82%) maintained normal QTc intervals. None of the subjects exhibited a clinically significantly prolonged QTc (>500 msec) or QTc dispersion >100 msec, and only 1 had a temporary clinically significant change from baseline (prolongation >60 msec). Furthermore, none of the participants were deemed to have clinically noteworthy cardiac changes or were discontinued from the study for such reasons. The mean and median methadone dose was 95 mg/d (range 50-130 mg/d).[23]

Closer inspection of data from this investigation reveals certain uncontrolled and confounding variables.[24] Prior to enrollment, 28% of subjects had a history of cardiovascular abnormalities and 20% had psychiatric diagnoses. During the MMT phase, 17% of subjects started concomitant medications. Although continued drug abuse declined during the study, 83% of drug screens were positive during the MMT phase – primarily opiates, cocaine, benzodiazepines, and alcohol.

The extent to which these potentially cardiotoxic agents might have contributed to QTc changes is unknown, although in view of continued substance abuse it is noteworthy that there were so few clinically relevant QTc elevations in this population. Also, the 30-day MMT period might have been insufficient for demonstrating methadone’s potential for eventually ameliorating QT prolongation, as was evident in the Stimmel et al. study.[22] Therefore, although this is the largest-scale ECG assessment in methadone-maintained patients, effects on the QTc interval associated solely with this medication are ambiguous.

There is still the question of whether methadone doses significantly higher than those typically used in many MMT programs might engender cardiac risks.[25,26] In a prior report, *A.T. Forum* developed a case series from one large MMT clinic profiling 12 patients receiving ≥ 500 mg/d of methadone (mean 812 ± 249 mg/d; range 500 - 1400 mg/d; see **Graph**).[4,27] All patients were taking comedications and many had physical illness, such as HIV, hepatitis, liver cirrhosis, hypertension, and diabetes; although, none of the patients had signs or symptoms of cardiac distress.



As might be expected, females exhibited higher mean QTc values than males (460 vs 422 msec). The overall mean QTc interval – 435 ± 45 msec – was within accepted limits. Only one patient, at 512 msec, had a QTc greater than the clinically significant threshold (500 msec). This was a 43 year old woman with hepatitis C, taking several medications, and receiving 1000 mg/d of methadone. She had never experienced symptoms of heart distress and, in fact, was an avid runner. An ECG ten years earlier, when she was receiving only 100 mg/d of methadone, had exhibited an identical QTc interval.[4] In contrast to the Krantz et al. cases,[1] this series implies that patients at higher methadone doses do not necessarily present greater risks, and additional prospective observations in patients administered doses at these levels would be appropriate.

Of further interest in the *A.T. Forum* series there was only a moderate, but nonsignificant, correlation between methadone dose and QTc interval ($r = 0.53$; $p = 0.08$).[4] In the *AIM* MMT

cases the dose-to-QTc association was even weaker ($r = 0.37$; $p = 0.32$), but this also was a small sample.[1] In the much larger study by Huber et al., the correlation also was weak and nonsignificant ($r = 0.20$; $p = 0.08$).[23] Methadone blood serum levels were not tested in the *A.T. Forum* or *AIM* case series; however, in the Huber et al. study, there were only very weak, nonsignificant associations between QTc changes and methadone peak or trough plasma levels, with correlation coefficients ranging from 0.01 to 0.18 ($p = 0.92 - 0.26$).[23,24]

These observations could be important, because a dose-response relationship influencing cardiac conduction, as demonstrated in the laboratory, would have been expected if methadone had clinically significant arrhythmogenic potential in humans. Symptomatic acquired LQTS often occurs within the first several days of starting a QT-prolonging drug,[28] and 3 of the Krantz et al. subjects had a methadone dose increase within one month prior to TdP (Table 1). However, the magnitude of increase, precise time proximity, and relationship to other events are not specified. Some researchers have noted that identifying factors influencing acquired TdP is challenging because it is a “moving target.” A patient may be at risk early in therapy or much later because of unreported or seemingly inconsequential circumstances, such as diarrhea leading to potassium loss or drinking grapefruit juice that interferes with drug metabolism.[29]

Better Education Needed

A year ago Krantz wrote in *A.T. Forum*, “There is no compelling evidence in the literature to suggest that methadone treatment is a direct cause of sudden cardiac death or fatal heart rhythm disturbances. [F]rom a cardiovascular perspective, methadone is a safe medication and MMT program staff can perform vital roles in providing effective cardiac risk-reduction services.”[7]

Cases of TdP in the presence of methadone now have been reported in the literature. An editorial comment accompanying the Krantz et al. *AIM* article notes: “These data suggest, but do not prove, that very-high-dose methadone can cause torsade de pointes.”[1] However, present evidence imputing methadone at any dose as a causative agent in TdP is too sparse and of inadequate quality even to be suggestive. In fact, an alternate hypothesis would propose that, due to calcium-channel-slowing effects, methadone may have a protective effect in preventing or delaying cardiac events that might otherwise occur in a high risk MMT population.

The anecdotal cases may serve as a reminder that methadone is a potent agent that must be prudently prescribed. If there are specific risks predisposing certain MMT patients to QTc prolongation and/or TdP or other arrhythmias it is vital to learn of them for early detection and ongoing monitoring purposes. Even if some factors, such as female gender or identified genetic predispositions cannot be modified, others such as electrolyte imbalances, potentially interacting medications, or ongoing substance abuse might be ameliorated once recognized.

In lieu of more definitive information, *A.T. Forum* has previously recommended action steps for minimizing cardiac risks in MMT patients,[2] and these are listed in **Table 3**. The small number of published case reports should not be a cause of great alarm or anxiety among patients receiving methadone, those prescribing it, or those regulating its use. A more appropriate and constructive response would be better education of physicians, staff, and patients regarding potential cardiac risk factors during MMT, including how to identify and manage them.

Table 3: Minimizing Cardiac Risks in MMT^[4]

- Patients entering MMT should be screened for cardiac risk factors and medical records for all patients should be periodically updated in this regard.
- Records should note prior heart problems and current heart health status, family history of heart conditions, past and current substances abused (including tobacco), and current medications (including OTC and herbal products).
- Patients with prior heart problems or significant current risk factors should be more closely monitored during MMT, particularly during the start-up induction phase and following significant dose increases.
- These patients should be educated on symptoms to watch for – e.g., “racing” heartbeat, dizziness, or fainting spells – and encouraged to contact the clinic immediately. Staff should be trained in handling such calls from patients.
- In some cases, it may be useful to perform baseline ECGs in patients with significant cardiac risk factors upon entering treatment or when they are prescribed medications with known cardiac effects. An ECG should be repeated to detect any significant changes.
- In patients taking comedications that have demonstrated harmful cardiac effects or interactions with other drugs, it might be advisable to adjust therapy (e.g., change in dose or medication) and/or to closely monitor those patients for adverse reactions.

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