

LESSONS LEARNED AT THE INTERFACE OF MEDICINE AND PSYCHIATRY

The Psychiatric Consultation Service at Massachusetts General Hospital (MGH) sees medical and surgical inpatients with comorbid psychiatric symptoms and conditions. Such consultations require the integration of medical and psychiatric knowledge. During their thrice-weekly rounds, Dr. Stern and other members of the Psychiatric Consultation Service discuss the diagnosis and management of conditions confronted. These discussions have given rise to rounds reports that will prove useful for clinicians practicing at the interface of medicine and psychiatry.

Drs. Abramson and Quinn are residents in psychiatry at MGH and McLean Hospital and clinical fellows in psychiatry at Harvard Medical School; Dr. Stern is chief of the Psychiatric Consultation Service at MGH and a professor of psychiatry at Harvard Medical School.

Dr. Stern has served as a consultant to Eli Lilly and Janssen and on the speakers or advisory boards for Forest, is a stock shareholder in WiFiMed Holdings, and has received royalties from Mosby/Elsevier and McGraw Hill. Drs. Abramson and Quinn report no financial or other relationships relevant to the subject of this article.

Corresponding author and reprints: Davin K. Quinn, M.D., Massachusetts General Hospital, Fruit St., WRN 605, Boston, MA 02114 (e-mail: dqquinn2@partners.org).

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Methadone-Associated QTc Prolongation: A Case Report and Review of the Literature

David W. Abramson, M.D.; Davin K. Quinn, M.D.;
and Theodore A. Stern, M.D.

Have you ever wondered what drugs or conditions lead to a lengthening of the QTc interval and to torsades de pointes (TdP)? Have you ever puzzled over how such problems can be managed? If so, then the following case vignette of a woman with prolongation of her QTc interval while taking methadone and other agents will provide a forum for the answers to these and other questions related to the workup and management of such symptoms.

Clinical Vignette

Ms. A, a 47-year-old woman with human immunodeficiency virus (HIV) infection (CD4 = 523 cells/ μ L, viral load < 50 copies/mL), hepatitis C, aspergillosis, and intravenous (IV) heroin use (on methadone maintenance for the last 12 years) was admitted to the hospital for a wedge resection of the right upper lobe for treatment of invasive pulmonary aspergillosis. Postoperatively, she developed a prolonged QTc and TdP.

At admission, Ms. A was on a highly active antiretroviral therapy (HAART) regimen of efavirenz (600 mg every night) and emtricitabine/tenofovir (200–300 mg/day) and had been receiving maintenance methadone. One year before she began HAART, her methadone dose (90 mg/day) had been stable for more than a decade, but since the initiation of efavirenz, the dose had progressively increased to 230 mg/day. An electrocardiogram (ECG) performed 3 days before admission showed a normal sinus rhythm (NSR) at 65 bpm, a QTc of 468 ms (normal < 450 ms), and normal intervals.

Ms. A underwent a right upper lobe lung wedge resection on the day of admission and was started on voriconazole therapy on the second hospital day. Her postoperative course was initially complicated by a spontaneous left-sided pneumothorax. Efavirenz was discontinued on hospital day 8, and she was started on treatment with raltegravir. On hospital day 11, Ms. A developed asymptomatic nonsustained ventricular tachycardia (NSVT); at that time, her serum potassium level was 3.5 mmol/L, and her magnesium level was 1.7 mmol/L. She had no known cardiac diseases, and her family history was devoid of arrhythmias. Furthermore, a transthoracic echocardiogram performed on hospital day 9 revealed no abnormalities. An ECG performed just after her NSVT revealed an NSR with a rate of 75 bpm, normal axes, and a normal QRS interval; the manually calculated QTc was prolonged (600 ms).

Ms. A was transferred to the cardiac step-down unit where she experienced a 12-second episode of TdP accompanied by a brief (1- to 2-second) loss of consciousness. She then had several episodes of NSVT and was started on amiodarone treatment. Isoproterenol therapy was started and titrated to achieve a heart rate of 90 to 100 bpm. While taking isoproterenol, Ms. A again had an episode of NSVT and another episode of TdP that required defibrillation. She remained on an isoproterenol drip from hospital days 11 through 24, when a pacemaker/automatic implantable cardioverter defibrillator (AICD) was implanted.

How Common Are QTc Prolongation and TdP in Patients Taking Methadone?

The QTc interval on the ECG corresponds to the interval between ventricular depolarization (Q wave) and completion of repolarization (T wave). Prolongation of the QTc interval is a marker of impending possibility of TdP and sudden death. A QTc duration > 450 ms is considered prolonged. In an analysis of patients with long QT syndrome, the risk of syncope or sudden death with a QTc < 446 ms is < 20%, whereas with a QTc > 498 ms, the risk is > 70%.¹ Unfortunately, the prevalence of QTc prolongation and TdP in methadone-treated patients is unclear. In part, this is because many cases of methadone-associated QTc prolongation and TdP never present for clinical evaluation, either because they are asymptomatic or because sudden death is the outcome. Deaths that were previously thought to be due to narcotics overdose and respiratory suppression may have been the result of sudden death.

Despite the association between methadone use and QTc prolongation, over a span of more than 30 years (1969–2002), only 43 cases of methadone-associated TdP and 16 cases of QTc prolongation have been reported to the U.S. Food and Drug Administration's MedWatch program.² Of these, only 1 individual was receiving less than 40 mg/day of methadone. The mean methadone dose in the reported cases was 410 mg/day (range, 29–1680 mg/day). Ten of the cases were within the recommended range for methadone maintenance (60–100 mg/day). Risk factors for QTc prolongation and TdP (e.g., taking medications with known drug-drug interactions, having a low potassium or magnesium level, having structural heart disease, or being female) were found in 75% of cases.²

Concern over QT prolongation and TdP associated with methadone use first emerged in 2002 when Krantz and colleagues³ (in a retrospective case series of 17 patients) reported TdP in patients receiving high-dose methadone (between 65 mg and 1000 mg/day). The treatment duration ranged from less than 1 month to more than 1 year. The QTc intervals of these patients ranged from 522 to 785 ms.³ Several case-control, cross-sectional, and prospective cohort studies have assessed the incidence of methadone-associated QT prolongation in patients on methadone maintenance therapy since that case series. Significant QT prolongation has been detected by these studies, but the rate of TdP has not been established.

Martell and colleagues in 2003⁴ conducted a prospective analysis of 132 heroin users who were started on methadone; they found a mean QTc increase of 10.8 ms (between baseline assessment and follow-up 2 months later). Subjects were stratified by dose; those who received the highest doses (110–150 mg/day) showed the largest increase in the QTc (13.2 ms). None of the sub-

jects showed an increase > 40 ms or developed TdP during the study. Thus, although an increase in the QTc reached statistical significance, the clinical significance of that increase remains unclear.⁴

In 2005, Martell and coworkers⁵ conducted a similar prospective study with longer follow-up periods (at 6 months and 12 months). Only 108 of 160 participants completed the 1-year follow-up. At 1 year, the mean increase in the QTc was 10.7 ms; 18% of the methadone users had a prolonged QTc (defined as > 450 ms for men and > 470 ms for women).⁵ Two participants had a QTc > 500 ms. A subset of patients (N = 44) had same-day serum methadone levels drawn. There was a statistically significant positive correlation between both peak and trough serum levels and QTc interval change between baseline and 1-year follow-up.⁵

In another long-term prospective study, Krantz and colleagues⁶ evaluated 118 methadone maintenance patients at program entry and at 6 months after the start of methadone therapy. Doses ranged from 20 to 180 mg/day. No occurrences of TdP were observed. The dose at 6 months was not associated with the magnitude of change in the QT. The QTc interval exceeded 450 ms in 31% of patients at 6 months. The magnitude of the effect appeared substantially less with methadone than with antiarrhythmics known to produce TdP.⁶

Cruciani and colleagues⁷ studied 104 patients receiving > 20 mg/day of methadone for more than 2 weeks (with a median dose of 110 mg/day, a range of 20–1200 mg/day, and a median duration of methadone use of 12.5 months). One third had QTc prolongation; however, no patients had a QTc longer than 500 ms. QTc prolongation was related to higher methadone doses and to shorter durations of treatment (in men). However, 25% of patients were also taking medications that could prolong the QTc.⁷

In another study by Ehret and colleagues,⁸ 167 hospitalized patients taking methadone were compared with 80 controls; 16.7% of the methadone-treated patients had a QTc interval > 500 ms, while none of the control group had a QTc > 500 ms. The QTc was weakly correlated with daily methadone dose. The average daily dose was 100 mg/day; the range was 6 to 400 mg/day.⁸ The QTc prolongation was associated with a higher daily methadone dose, a lower potassium level, a lower prothrombin level, and comorbid use of cytochrome P450 (CYP) 3A4 inhibitors. QTc prolongation was less common with methadone doses < 40 mg/day.⁸

In a more recent cross-sectional analysis, Fanoë and associates⁹ examined 452 individuals undergoing methadone treatment in Copenhagen, Denmark; they found that one third of methadone users (taking 100 mg/day) had a prolonged QTc interval (i.e., > 440 ms). However, only 8 individuals (2%) had a QTc > 500 ms, the level at which one's risk for TdP substantially increases.⁹

In summary, the capability of methadone to prolong the QTc at doses within the therapeutic range is well established in multiple studies, and the prevalence may range between 16% and 33%; however, it is not yet clear what dose of methadone causes clinically significant QTc prolongation or TdP.

What Conditions or Coadministered Medications Predispose Methadone Users to QTc Prolongation and TdP?

Methadone inhibits the rapid component of the iKr potassium channel encoded by the hERG or KCNH2 gene, which is a well-described mechanism for drug-induced QT prolongation.¹⁰ However, the occurrence of a prolonged QTc or TdP in methadone users is not due solely to the direct effect of methadone; comorbid conditions commonly contribute.

Risk factors for QTc prolongation in methadone users include older age, female gender, cardiac disease, antidepressant use, and HIV infection, as well as a higher daily methadone dose, a lower potassium level, a lower prothrombin level, and concomitant use of CYP3A4 inhibitors.^{2,5,8,11}

Other drugs of abuse, such as alcohol and cocaine, have been associated with prolonged QTc.¹² Structural heart disease (e.g., myocardial infarction, congestive heart failure, valvular disease, and cardiomyopathy), receiving higher than average drug dosing, having a prolonged QTc at baseline, having a family history of congenital QTc prolongation, and having a history of drug-induced TdP all increase the risk of subsequent QTc prolongation and TdP. Finally, treatments (e.g., antidepressants, antipsychotics, antiretrovirals, and antibiotics) administered for other comorbid conditions have been associated with prolongation of the QT. Medications (e.g., diuretics, laxatives, or mineralocorticoid hormones) that lower serum potassium and/or magnesium concentrations can also lower the threshold and lead to development of TdP. Table 1 lists risk factors for QTc prolongation.^{2,4,5,6,8,11}

The risk of TdP in methadone users is mediated by drug-drug interactions in 2 ways, pharmacodynamic (via a combined effect) and pharmacokinetic (involving an alteration of breakdown). Many medications (both legal and illicit) can independently prolong the QTc. These drugs, when given along with methadone, may synergistically increase the risk of TdP (Table 2).¹³ Among these agents are the commonly used medications amiodarone, chlorpromazine, cisapride, clarithromycin, droperidol, erythromycin, haloperidol, pentamidine, pimozide, procainamide, quinidine, sotalol, thioridazine, quinolone antibiotics, and antifungals.¹³

With regard to pharmacokinetics, methadone is primarily metabolized by the CYP3A4 enzyme and to a lesser degree by CYP2B6. Medications that induce or

Table 1. Risk Factors for QTc Prolongation

Risk Factor
Older age
Female gender
Structural heart disease
HIV infection
Low potassium level
Low prothrombin level
Higher methadone dose
Cytochrome P450 3A4 inhibitor use
Alcohol use
Cocaine use
Prolonged baseline QTc
Family history of prolonged QTc
History of drug-induced torsades de pointes
Antidepressant use
Antipsychotic use
Antiretroviral use
Antibiotic use
Potassium-lowering agent use
Magnesium-lowering agent use

inhibit this enzyme can increase or decrease the serum concentrations of methadone. Strong CYP3A4 inhibitors include HIV antivirals (e.g., indinavir, nelfinavir, and ritonavir), as well as antibiotics and antifungals (e.g., clarithromycin, itraconazole, and ketoconazole). Efavirenz is known as an inducer of CYP3A4. In the case of Ms. A, her methadone levels likely increased when an inducer was removed from her regimen and an inhibitor was introduced; Tables 3 and 4 list enzyme substrates, inducers, and inhibitors.¹⁴

Gil and colleagues¹⁵ reported on 4 HIV-infected patients who presented with syncope while receiving HAART and high doses of methadone (> 200 mg/day); they each had a prolonged QTc, and 1 had TdP. When HAART is instituted, methadone doses often need to be increased due to the induction of metabolism by CYP3A4. When HAART is discontinued, methadone dosing should be decreased as levels will tend to rise.

Are QTc Prolongation and TdP Also Associated With Use of Other Narcotics?

One synthetic derivative of methadone, levomethadyl, was linked with elevated rates of QTc prolongation and TdP¹⁶; as a result, it was taken off the European market in 2003. However, in general, QTc prolongation is not considered a consequence of use of other narcotics. No reports of QTc prolongation were found in buprenorphine users in the Copenhagen cross-sectional study.⁹ In a randomized, controlled trial of 179 opiate abusers taking methadone, buprenorphine, or levomethadyl, none taking buprenorphine had an increase of their QTc (defined as > 470 ms).¹⁷

Further, in a study comparing patients receiving IV methadone and morphine, a dose-dependent increase in QTc interval was observed for those receiving methadone

Table 2. Drugs That Prolong QTc and Increase Risk of TdP^a

Drug	Indication for Use	Comments
Amiodarone	Antiarrhythmic/abnormal heart rhythm	Females > males, TdP risk regarded as low
Arsenic trioxide	Anticancer/leukemia	
Astemizole	Antihistamine/allergic rhinitis	No longer available in the United States
Bepridil	Antianginal/heart pain	Females > males
Chloroquine	Antimalarial/malaria infection	
Chlorpromazine	Antipsychotic/antiemetic/schizophrenia/nausea	
Cisapride	GI stimulant/heartburn	Restricted availability, females > males
Clarithromycin	Antibiotic/bacterial infection	
Disopyramide	Antiarrhythmic/abnormal heart rhythm	Females > males
Dofetilide	Antiarrhythmic/abnormal heart rhythm	
Domperidone	Antinausea/nausea	Not available in the United States
Droperidol	Sedative, antinausea/anesthesia adjunct, nausea	
Erythromycin	Antibiotic, GI stimulant/bacterial infection, increase GI motility	Females > males
Halofantrine	Antimalarial/malaria infection	Females > males
Haloperidol	Antipsychotic/schizophrenia, agitation	When given intravenously or at higher-than-recommended doses, risk of sudden death, QT prolongation, and TdP increases
Ibutilide	Antiarrhythmic/abnormal heart rhythm	Females > males
Levomethadyl	Opiate agonist/pain control, narcotic dependence	
Mesoridazine	Antipsychotic/schizophrenia	
Methadone	Opiate agonist/pain control, narcotic dependence	Females > males
Pentamidine	Antifective/pneumocystis pneumonia	Females > males
Pimozide	Antipsychotic/Tourette's tics	Females > males
Probucol	Antilipemic/hypercholesterolemia	No longer available in the United States
Procainamide	Antiarrhythmic/abnormal heart rhythm	
Quinidine	Antiarrhythmic/abnormal heart rhythm	Females > males
Sotalol	Antiarrhythmic/abnormal heart rhythm	Females > males
Sparfloxacin	Antibiotic/bacterial infection	
Terfenadine	Antihistamine/allergic rhinitis	No longer available in the United States
Thioridazine	Antipsychotic/schizophrenia	

^aAdapted with permission from Arizona Center for Education and Research on Therapeutics.¹³ Readers should check for updates at www.qtldrugs.org/medical-pros/drug-lists/bycategory.cfm, as the information is subject to frequent change. Abbreviations: GI = gastrointestinal, TdP = torsades de pointes.

but not for those receiving morphine.¹⁸ In another study comparing methadone with morphine,¹⁹ 8 chronic pain patients were switched from morphine to oral methadone (with an average dose between 51 and 57 mg/day); there was a minor but statistically significant increase in the QTc (but without a clinical correlation) for patients switched to methadone.

How Should QTc Prolongation and TdP Be Monitored in a Patient Taking Methadone?

Before starting methadone, a 12-lead ECG (with calculation of the QTc interval) should be obtained. The tracing should be repeated at regular intervals, although there is no consensus about what the frequency of these intervals should be. QTc prolongation can occur within days of initiating methadone therapy; therefore, we recommend repeating ECG testing as early as 2 weeks after initiation.

Unfortunately, there is not enough evidence to assert that serum methadone levels should be checked to predict QTc prolongation. Martell and coworkers in 2005⁵ measured serum methadone levels as part of their prospective study of 108 methadone users and found the serum concentration of methadone correlated well with the QTc. However, in a cross-sectional study of 138 patients by

Peles and associates,²⁰ there was no correlation between methadone dose, serum methadone level, and the QTc. Only 3 of 138 patients had a prolonged QTc (defined as > 500 ms). Further studies are needed to determine which serum concentration levels of methadone significantly prolong the QTc.

Eap and associates²¹ found that variation in the ability of the enzyme CYP2B6 to metabolize the S-enantiomer of methadone can increase the risk of QTc prolongation (by a factor of 4.5) while taking methadone. This is due to the S-enantiomer's property of blocking hERG voltage-gated potassium channels in human cells; slow metabolizers of the S-enantiomer are at higher risk for QTc prolongation. This may become a worthwhile test to predict which methadone users will develop QTc prolongation.

In the Case of Ms. A, Which Factors Most Likely Contributed to the Development of QTc Prolongation and TdP?

Ms. A had several risk factors that predisposed her to development of QTc prolongation, including female gender, HIV-positive status, and the drug-drug interaction of her medications. Although Ms. A had been taking a stable dose of 90 mg/day of methadone for approximately

Table 3. Cytochrome P450 3A4 Substrates^a

Substrates	
Macrolides	Miscellaneous
Clarithromycin	Alfentanil
Erythromycin	Aprepitant
Telithromycin	Aripiprazole
Antiarrhythmics	Buspirone
Quinidine	Cafegot
Benzodiazepines	Caffeine
Alprazolam	Cilostazol
Diazepam	Cinacalcet
Midazolam	Cocaine
Triazolam	Codeine
Immune modulators	Dapsone
Cyclosporine	Dexamethasone
Tacrolimus	Dextromethorphan
HIV antivirals	Docetaxel
Indinavir	Domperidone
Nelfinavir	Eplerenone
Ritonavir	Fentanyl
Saquinavir	Finasteride
Prokinetic	Gleevec
Cisapride	Haloperidol
Antihistamines	Irinotecan
Astemizole	Lapatinib
Chlorpheniramine	Levomethadyl
Terfenadine	Lidocaine
Calcium channel blockers	Methadone
Amlodipine	Nateglinide
Diltiazem	Ondansetron
Felodipine	Pimozide
Lercanidipine	Propranolol
Nifedipine	Quetiapine
Nisoldipine	Quinine
Nitrendipine	Risperidone
Verapamil	Salmeterol
Statins	Sildenafil
Atorvastatin	Sirolimus
Cerivastatin	Tamoxifen
Lovastatin	Taxol
Simvastatin	Terfenadine
Steroid products	Trazodone
Estradiol	Vincristine
Hydrocortisone	Zaleplon
Progesterone	Ziprasidone
Testosterone	Zolpidem

^aBased on Flockhart.¹⁴

12 years, when she began taking efavirenz approximately 1 year earlier, her daily methadone dose was increased to 230 mg/day. Efavirenz, an inducer of the CYP3A4 enzyme (which is the primary enzyme involved in the metabolism of methadone), lowered the effective serum concentration of methadone. Efavirenz was discontinued on hospital day 3; this likely led to an increase in serum levels of methadone. Further, on hospital day 2, Ms. A was started on voriconazole for aspergillus infection. Voriconazole also may increase the effective serum concentration of methadone, as it is an inhibitor of the CYP3A4 enzyme, in addition to having intrinsic QTc-prolonging capability.

In summary, while an enzyme inducer was removed and an inhibitor was added, Ms. A's methadone dose was

Table 4. Cytochrome P450 3A4 Inhibitors and Inducers^a

	Inhibitors	Inducers
HIV antivirals	H2 antagonists	HIV antivirals
Delavirdine	Cimetidine	Efavirenz
Indinavir	Antimicrobials	Nevirapine
Nelfinavir	Chloramphenicol	Stimulants
Ritonavir	Norfloxacin	Modafinil
Saquinavir	Chelators	Glucocorticoids
Antifungals	Diethyldithiocarbamate	Anticonvulsants
Fluconazole	Contraceptives	Barbiturates
Itraconazole	Gestodene	Carbamazepine
Ketoconazole	Mifepristone	Oxcarbazepine
Voriconazole	Tyrosine kinase inhibitor	Phenobarbital
Macrolides	Imatinib	Phenytoin
Clarithromycin	Antidepressants	Antitubercular agents
Erythromycin	Fluvoxamine	Rifabutin
Telithromycin	Nefazodone	Rifampin
Antiemetic	Norflouxetine	Herbal supplements
Aprepitant	Foods	St. John's wort
Calcium channel blockers	Grapefruit juice	Thiazolidinediones
Amiodarone	Star fruit	Pioglitazone
Diltiazem		Troglitazone
Mibefradil		
Verapamil		

^aBased on Flockhart.¹⁴

left unchanged; this resulted in a massive increase in her serum methadone level. She did not manifest any systemic symptoms of opiate intoxication such as altered mental status or decreased respiratory rate. On hospital day 14, 3 days after an episode of TdP (and while taking 210 mg/day of methadone), Ms. A's serum level was measured as 1636 ng/mL (reference range, 100–400 ng/mL). An increased serum methadone level, in combination with voriconazole, is most likely what led to Ms. A's prolonged QTc and TdP.

The case of Ms. A illustrates several important points with regard to the risk of developing QTc prolongation and TdP while taking methadone. First, if a patient is taking a drug that may alter the serum level of methadone, and the dose of this medication is changed, the dose of methadone may also need to be adjusted. Second, special caution should be taken when a medication that can prolong the QTc is added to the regimen of a patient already taking methadone. In either case, serial ECGs should be obtained to monitor for QTc prolongation. Anecdotal data, such as provided in our case, suggest that ECG changes can occur within days of medication adjustments. In sum, comorbidity is common among methadone users, and they are often taking other medications that affect methadone levels; as the QTc lengthens, so does the risk of TdP.

What Treatments Are Available in Cases of Methadone-Induced QTc Prolongation and TdP?

After an AICD was placed and her methadone tapered and discontinued, Ms. A was started on buprenorphine/

naloxone (and the dose was increased to 16 mg/day by the time of discharge). She tolerated the medication well and reported relief from symptoms of opiate withdrawal. From hospital day 26 until discharge (day 31), Ms. A's QTc was 420 to 430 ms. Ms. A continued to take voriconazole 200 mg twice/day and her HAART regimen (emtricitabine/tenofovir 200 mg/300 mg per day and raltegravir 400 mg twice/day).

If the etiology of QTc prolongation and TdP is an increased serum methadone level (in the context of altered metabolism), then it is reasonable to lower the methadone dose. Since Ms. A had been maintained on methadone for more than a decade without evidence of cardiac complications, her risk of having a prolonged QTc interval solely from methadone use was significantly diminished. However, Ms. A's prolonged QTc may also have resulted from the independent potential of voriconazole to prolong the QTc. Even lowering the dose (and serum level) of methadone might not have been sufficient (or safe) given Ms. A's need to continue with voriconazole treatment.

Buprenorphine may be used as an alternative to methadone as an opiate maintenance treatment. Wedam and colleagues in 2007¹⁷ demonstrated that buprenorphine when compared to methadone less often resulted in a prolonged QTc. In fact, none of the participants in the buprenorphine group developed a prolonged QTc compared to 23% in the methadone group. This is not to say that use of buprenorphine poses no risk for QTc prolongation, as 2% developed QTc increases > 60 ms (compared to 12% in the methadone group).¹⁷

In 2005, Krantz and colleagues⁶ reported the case of a woman who developed TdP while taking high-dose methadone (450 mg/day) and fluvoxamine; she was later transitioned to buprenorphine/naloxone. Her prolonged QTc (582 ms) decreased (to 395 ms) after methadone was discontinued. She was then started on buprenorphine/naloxone, and the dose was titrated to 32 mg/day. At 1-month and 2-month follow-up, her QTc was 425 ms and 408 ms, respectively. These results suggest that buprenorphine was less likely to cause QTc prolongation than methadone, even in a person who had demonstrated susceptibility to the effects of methadone. As already mentioned, induction with buprenorphine was still followed by an increase in the QTc.⁶

Finally, Baker and associates in 2006²² published an open-label, prospective trial examining the effect of HAART and buprenorphine on the QTc. Fifty HIV-positive, opiate-dependent subjects were titrated on buprenorphine (range, 16–20 mg/day) and then were stabilized on 1 of 5 antiretroviral treatments (efavirenz, nelfinavir, delavirdine, ritonavir, or lopinavir/ritonavir). Electrocardiograms were performed at baseline after subjects had taken buprenorphine for 2 weeks and again after HAART had been administered at steady state (for 5–15

days). In the study, the authors found that buprenorphine alone did not cause QTc lengthening but that buprenorphine in combination with an antiretroviral caused a significant increase in the QTc.²² However, the increase in QTc was driven by 2 antiretrovirals (delavirdine and ritonavir). Moreover, although statistically significant, the absolute value was not clinically significant. No individual had an increase of the QTc (> 50 ms, which was the a priori cutoff for clinically significant change).²²

Another treatment option is placement of an AICD/pacemaker. Patel and coworkers in 2008²³ published a case series of 8 patients who underwent AICD placement after episodes of methadone-associated TdP. The series reported that 3 of the 8 people who continued taking methadone after placement received shocks for detected TdP within the 2-year follow-up. Thus, the procedure was heralded as potentially life saving for people with a history of TdP who continue to take methadone.²³ However, 1 of the 8 patients died of unknown causes, and 2 of the 8 patients suffered serious perioperative complications (pericardial tamponade and device infection). Thus, although promising, the full risks and benefits of AICD placement in this patient population are not known.²³

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