ADDICTION TREATMENT

Forum

Cardiac Considerations During MMT*

*Methadone Maintenance Treatment

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Overview

Some patients in methadone maintenance treatment (MMT) programs may have conditions or behaviors associated with increased risks of arrhythmia, including: abuse of cardiotoxic substances, cardiovascular disease, electrolyte imbalances, and prescribed medications that may foster cardiac repolarization disturbances. Furthermore, recent data suggest that in some individuals methadone – alone or, more commonly, in combination with other drugs and/or cardiac risk factors – can prolong the QT interval. This may contribute to the development of the serious arrhythmia torsade de pointes (TdP) in susceptible patients.

Current evidence, however, is insufficient to support altering routine dosing practices or requiring electrocardiograms (ECGs) for all patients entering or continuing MMT and should not deter the appropriate use of methadone. The relatively small potential risk of adverse cardiac effects with methadone should be weighed against the serious risks of withholding MMT; including a high likelihood of illicit drug use and its related morbidity, mortality, and public health ramifications.

This paper briefly summarizes the published research concerning methadone affects on cardiac repolarization and TdP. Clinical suggestions are offered in identifying individual patient cardiac risk factors and for optimizing cardiac safety during MMT.

Heightened Concerns

The medical community and government agencies have raised concerns about medications associated with prolongation of the QT interval on the electrocardiogram (ECG). This alteration in cardiac repolarization may result in a serious and potentially fatal arrhythmia known as torsade de pointes (TdP; *see **Side Box** for a review of the QT and TdP*).

Particular concerns relating to medications used in the treatment of opioid addiction surfaced in 2001 and focused on 10 patients administered LAAM (levacetylmethadol or Orlaam®) who developed cardiac electrophysiologic disturbances: QT interval prolongation and/or TdP. LAAM was subsequently withdrawn from European markets (EMEA 2001). In the United States, the FDA strengthened warnings about this arrhythmogenic potential (FDA 2001) and screening ECGs were recommended prior to and during LAAM titration (AATOD 2001). Finally, in late August 2003, the U.S. manufacturer of LAAM announced plans to discontinue the product.

Although LAAM differs from methadone by its much longer half-life and multiple active metabolites, there was speculation that methadone also might affect cardiac repolarization (EMEA 2001). Further interest has been stimulated by laboratory research, case reports, and clinical studies exploring the cardiac effects of methadone. This paper briefly summarizes those published findings and provides suggestions for optimizing cardiac safety in patients starting and/or continuing methadone maintenance treatment (MMT).

Methadone Effects on Repolarization

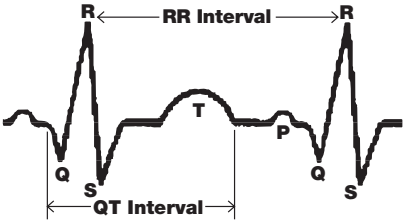
Oral methadone, when administered appropriately and in adequate doses as part of an MMT program, is the most effective therapy for opioid addiction and has been associated with a reduction in mortality in observational studies (Langendam et al. 2001). It has been prescribed for more than 35 years, in millions of patients, worldwide and has demonstrated a favorable safety profile (Kreek 1973; Novick et al. 1993).

Manufacturers' package inserts for methadone products have acknowledged possible cardiac-related side effects, such as: bradycardia, palpitations, hypotension, faintness, and syncope (Mallinckrodt 2000; Roxane 2000). Future product information

Side Box: A Review of QT, QTc, and TdP

Electrical currents regulate heart rhythm in an orderly and time-sensitive fashion, and their disruption can lead to arrhythmias. An electrocardiogram (ECG) measures electrical conduction through the heart during each beat, and an important portion of the characteristic waveform is the QT interval (see ***Figure***), which denotes cardiac depolarization and repolarization.

Measured in fractions of a second or milliseconds (msec), the QT interval is one indicator of healthy heart function. Prolongation of the QT interval to greater than normal length is considered a possible sign of impending arrhythmia.



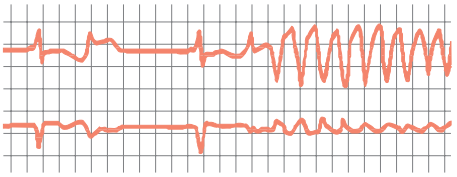
Heart rate affects QT length, so the QT measurement is usually corrected for this and expressed as QTc (QT-corrected) using Bazett's formula: QTc = QT in msec divided by the square root of the RR interval between beats in seconds. This way, comparisons can be made independent of heart rate; although, heart rates between 50 and 75 beats per minute are necessary for accurate interpretation.

Accurate measurement of the QT interval is complicated by a lack of standardization in ECG recorders and subtle changes in waveforms. Patient factors also affect QT length: e.g., depleted electrolyte levels, physical illness, drug or alcohol consumption, postural changes during recording, and time of day the ECG is recorded. Also, QTc intervals may be 10% longer in women than men until age 50. This diversity of factors can make it difficult to interpret the significance of QTc lengthening in individual patients.

The upper limits of normal QTc values are roughly 440 msec in men and 460 msec in women. Numerous authorities have suggested that QTc values of 500 msec or more, or increases of greater than 60 msec from baseline, indicate significant risk of arrhythmia. However, less severe QTc prolongations (460-500 msec) may be important, depending on individual patient cardiac risk factors.

An abnormally prolonged QTc interval associated with arrhythmia is referred to as *Long QT Syndrome* or *LQTS*. It can be an inherited condition involving defects in genes that control repolarization channels in heart muscle (*congential LQTS*), or it may be caused by certain drugs or toxins, reduced levels of electrolytes (e.g., potassium or magnesium), or certain physical ailments. This is known as *acquired LQTS*.

When the QTc becomes prolonged, patients may occasionally develop a rapid, abnormal heart rhythm called polymorphic ventricular tachycardia (known as torsade de pointes [TdP], a French phrase meaning "twisting of the points"). The ECG waveform displays a series of undulating peaks twisting about a central axis (*right side of* ***Figure***).



During a TdP episode, sometimes triggered by extremes of heart rate, the person may experience palpitations, or dizziness. In more severe cases, the individual may faint (syncope) or have what appears as a seizure due to insufficient blood flow to the brain. TdP often resolves on its own, with a return to normal heart rhythm. However, further TdP episodes may quickly follow and occasionally degenerate into ventricular fibrillation (convulsive twitching of heart muscle), causing death if the person is not resuscitated.

Sources: Al-Khatib et al. 2003; Bonate and Russell 1999; DePonti et al. 2000; Ebert et al. 1998; El-Sherif and Turitto 1999; Hampton 2003; Haverkamp et al. 2002; Janeira 1995; Leavitt 2001; Morganroth 1993; Vincent 2000; Vincent et al. 1999; Welch and Chue 2000; Wolbrette and Patel 1999.

will likely recognize methadone's potential association with QT-interval prolongation and TdP, since a number of investigations describing those adverse effects have appeared in the scientific literature.

Laboratory Studies

At least ten experiments have demonstrated effects of high-concentration methadone on cardiac electrophysiology in various isolated cell and tissue types (reviewed in Leavitt 2001). Recent laboratory evidence suggests that methadone may delay cardiac repolarization by blocking potassium currents (Katchman et al. 2002), which has the potential for contributing to arrhythmia, mainly TdP (Tomargo, 2000).

Case Reports

Much of the evidence to date suggesting that oral methadone influences QTc prolongation and the potential for inducing TdP has involved case reports and small case series (28 cases total – Bittar et al. 2002; De Bels et al. 2003; Krantz et al. 2002, 2003; Mokwe and Ositadinma 2003; Sala et al. 2003; Walker et al. 2003). Many cases (39%) involved methadone used for analgesia and in 82% (23/28) of all incidents additional factors could have played important roles in triggering QT-prolongation or TdP. Also, underlying genetic predispositions to arrhythmia in these cases could not be excluded, and such hereditary factors are being increasingly recognized in what was thought to be acquired LQTS (Hampton 2003; Vincent 2000).

In the 17 cases of TdP in methadone-treated patients reported by Krantz and colleagues (2002) 14 had known risk factors for QT prolongation, such as hypokalemia or were taking other drugs that might prolong the QT interval. In two recent cases described by De Bels et al. (2003), the subjects were taking multiple substances of abuse, particularly cocaine, which is known to cause TdP (Lange and Hillis 2001). In recent cases from Sala et al. (2003), four male patients receiving methadone and developing prolonged QTc intervals (mean 590 msec) were HIV-positive and administered additional medications that may have affected cardiac repolarization or altered serum methadone concentrations. Walker et al. (2003) reported TdP in three patients treated with methadone for chronic pain; interactions with other potentially QT-prolonging medications were possible in all three, and in two cases underlying congestive heart failure (a major risk for TdP) was present. All of these cases are a reminder that acquired LQTS and TdP often result from a confluence of multiple arrhythmia risk factors, rather than a single causative agent.

Clinical Investigations

Past clinical investigations demonstrated relatively modest effects of oral methadone on cardiac repolarization during MMT (Huber et al. 2001; Stimmel et al. 1973). In a recently reported retrospective study of 50 pain patients, there was no change in QTc interval during oral methadone therapy (Reddy et al. 2003). However, in a recent prospective observational trial in 132 patients there was a small but statistically significant prolongation of the QTc interval during early stages of MMT (overall mean increase 10.8 msec; p <0.001). There was substantial polydrug abuse among the subjects besides heroin (including alcohol, sedatives, and cocaine), the *clinical* significance of such small QT increases was uncertain, as none of the subjects developed cardiac arrhythmia (Martell et al. 2003). Additional clinical research is underway.

Dose-Response Effects

Correlations of methadone dose and QTc prolongation have been mixed. Huber et al. (2001) found a weak, nonsignificant relationship (r = +.20), while Krantz et al. (2003) reported a statistically significant though modest correlation (r = +.51) and noted that methadone might not have been the primary factor affecting QT-prolongation. Leavitt (2001) reported a similar moderate, but statistically nonsignificant, correlation (r = +.53) in a series of 12 patients at methadone doses of 500 mg/d or more and, similar to the Krantz et al. (2003) series, there were prominent inter-individual differences.

An important question is whether methadone doses significantly higher than those typically used in many MMT programs might carry greater cardiac risks. In the Krantz et al. TdP cases (2002), doses ranged from 65 to 1000 mg/d, with most greater than 200 mg/d (average 397 mg/d). Similarly, the dose ranged from 275 to 500 mg/d (mean 365 mg/d) in the four Sala et al. (2003) cases and from 650 to 880 mg/d (mean 743 mg/d) in the three Walker et al. (2003) cases.

However, the clinical study by Martell and colleagues (2003) found that the increase in QTc interval was only marginally greater in patients receiving methadone doses ranging from 110 to 150 mg/d compared with those receiving 0 to 59 mg/d (13.2 vs 11.1 msec, respectively). In a small case series involving 12 patients receiving from 500 to 1400 mg/d (mean 812 mg/d), the average QTc interval was 435 msec (Leavitt 2001).

As an additional consideration, it might be expected that the serum methadone level (SML) could better predict effects on cardiac repolarization than the dose itself. However, to date, only Huber et al. (2001) examined SMLs in this context, and they found only slight, statistically nonsignificant correlations of peak *or* trough SMLs with QTc values (maximum r = +.18; p = 0.26).

Prolonged QTc interval and TdP in MMT patients may depend on various factors, with high methadone doses or serum levels playing still undetermined roles. At the same time, however, it is important that adequate methadone doses continue to be appropriately administered for successful substance-abuse treatment outcomes (Leavitt 2003).

Arrhythmia Risk in MMT Patients

It is important for practitioners to be aware of medical conditions and medications that might influence the development of QT prolongation during methadone maintenance, as discussed below. However, these should not be used to automatically exclude patients from entering or continuing MMT. Although some factors cannot easily or quickly be corrected, others might be modified and/or closely monitored during methadone maintenance.

Predisposing Conditions

According to current data, cardiovascular disease ranks as the number one cause of death in the overall population (AHA 2003). There are an estimated 300,000 to 400,000 sudden cardiac deaths each year in the U.S., with most due to ventricular arrhythmias (Hampton 2003).

Drug-addicted persons in general – including those entering or already in MMT programs – can be at risk of arrhythmia due to abuse of cardiotoxic substances, such as cocaine, amphetamines, and alcohol (Hser et al. 2001). Cocaine has long been recognized as toxic to the heart; blocking sodium and potassium channels, depressing cardiac function, and causing both TdP and myocardial infarction (Lange and Hillis 2001). The QTc may be prolonged in up to 20% of patients who abuse alcohol (Mathot et al. 2000; Takehana and Izumi 2000).

Patients also can have other substance abuse related cardiac disorders predisposing to arrhythmia, including: cardiomyopathy (often due to alcohol or cocaine abuse); infectious endocarditis (due to injection drug use), which may result in chronic valvular disease and myocardial dysfunction; and, coronary artery disease or pulmonary-associated heart disease (possibly associated with habitual tobacco and/or marijuana smoking). Additional arrhythmia-risk factors may be present just as in the general population: congenital LQTS, electrolyte disturbances, altered nutritional states, myocardial ischemia, cardiac hypertrophy or dysfunction, and extremes of heart rate (Al-Khatib et al. 2003; Crouch et al. 2003; Dressler and Roberts 1989; Reilly et al. 2000; Welch and Chue 2000).

Certain medications, particularly psychiatric drugs, account for many cases of *acquired* LQTS and may induce TdP (Drici and Barhanin 2000; Welch and Chue 2000), and patients who develop TdP due to a particular drug often have additional risk factors predisposing to arrhythmia (Crouch et al. 2003). This is critical in the MMT population where dual psychiatric diagnoses are common and patients are frequently treated with multiple medications that may in themselves alter cardiac repolarization (Goodnick et al. 2002; Khawaja and Feinstein 2003; Leavitt 2001; Mathot et al. 2000). There is an ongoing need to consider risk-benefit relationships of multidrug administration and to choose alternate drug therapies when possible that are not cardiotoxic.

Drug *interactions* can be a further critical risk factor for QT prolongation and TdP (El-Sherif and Turitto 1999; Moss 2003; Priori 1998). Methadone is metabolized primarily by cytochrome P450 liver enzymes and may be affected by other medications that are metabolized by or inhibit the same enzymes. This can result in excessive accumulations of methadone and/or the other agents that could predispose to TdP in some cases (Eap et al. 2002; Leavitt 2001; Leavitt et al. 2000).

Table 1 presents a list of drugs that may influence QT prolongation and/or TdP, and those also having potential for metabolic interactions with methadone are so indicated. Some of those drugs are common and important components of medical regimens for MMT patients, and the list is intended to alert clinicians to potential interactions without suggesting that the medications should be routinely avoided in all patients receiving methadone. Consideration also should be given to concomitant

drugs capable of inducing hypokalemia or hypomagnesemia as they might precipitate QT prolongation and interact with methadone and/or drugs listed in the Table. These include diuretics, laxatives, and in rare cases mineralocorticoid hormones.

Table 1: Drugs That May Predispose to Prolonged QTc or TdP (alphabetical order)

adenosine (Adenocard)[C]
amantadine (Symmetrel)[B]
amiodarone (Cordarone)[A]#
amitriptyline (Elavil)[C]#
arsenic trioxide (Trisenox)[A]
astemizole (Hismanal)[C]#
bepridil (Vascor)[A]
chlorpromazine (Thorazine)[A]#
cisapride (Propulsid)[A]#
citalopram (Celexa)[C]
clarithromycin (Biaxin)[A]#
desipramine (Norpramin)[C]
disopyramide (Norpace)[A]#
dofetilide (Tikosyn)[A]
dolasetron (Anzemet)[B]
domperidone (Motilium)[A]
doxepin (Sinequan)[C]
droperidol (Inapsine)[A]
erythromycin (EES, Erythrocin)[A]#
felbamate (Felbatol)[B]
flecainide (Tambocor)[B]#
fluoxetine (Prozac)[C]#
foscarnet (Foscavir)[B]
fosphenytoin (Cerebyx)[B]
gatifloxacin (Tequin)[B]
granisetron (Kytril)[B]
halofantrine (Halfan)[A]
haloperidol (Haldol)[A]#
ibutilide (Corvert)[A]
imipramine (Tofranil)[C]#
indapamide (Lozol)[B]
isradipine (DynaCirc)[B]
ketoconazole (Nizoral)[C]#
levomethadyl (Orlaam)[A]#
levofloxacin (Levaquin)[B]
lithium (Eskalith, Lithobid)[B]
maprotiline (Ludiomil)[C]
mesoridazine (Serentil)[A]
methadone (Disket, Dolophine, Methadose)[A]
moexipril/HCTZ (Uniretic)[B]
moxifloxacin (Avelox)[B]
naratriptan (Amerge)[C]
nicardipine (Cardene)[B]
nortriptyline (Aventyl. Pamelor)[C]#
octreotide (Sandostatin)[B]
ondansetron (Zofran)[B]#
paroxetine (Paxil)[C]#
pentamidine (Pentam, NebuPent)[A]
pimozide (Orap)[A]
procainamide (Procan, Pronestyl)[A]
propafenone (Rythmol)[C]
quetiapine (Seroquel)[B]
quinidine (Cardioquin, Quinaglute)[A]#
risperidone (Risperdal)[B]
rizatriptan (Maxalt)[C]
salmeterol (Serevent)[B]#
sertraline (Zoloft)[C]#
sotalol (Betapace)[A]
sparfloxacin (Zagam)[A]
sumatriptan (Imitrex)[C]
tacrolimus (Prograf)[B]
tamoxifen (Nolvadex)[B]#
telithromycin (Ketek)[B]
thioridazine (Mellaril)[A]#
tizanidine (Zanaflex)[B]
venlafaxine (Effexor)[B]#
voriconazole (Vfend)[B]
ziprasidone (Geodon)[B]
zolmitriptan (Zomig)[C]

A. Drugs with *known* risk of TdP (Haverkamp et al. 2000; Woosley 2003).
B. Drugs with a *suspected* risk of TdP (Woosley 2003).
C. Drugs that *may possibly* influence QT prolongation (LQT); additional agents have been *proposed* as possibly influencing LQT but are not listed (Al-Khatib et al. 2003; Crouch et al. 2003; Goldschlager et al. 2003).
= Drugs metabolized by or inhibitors of enzymes involved in methadone metabolism – CYP-3A4, -2D6, and/or -1A2 (Crouch et al. 2003; Flockhart 2003).
Brand names (in parentheses) are registered trademarks of their respective manufacturers. Some products may be marketed under additional brand names.

Lists such as Table 1 can serve only as a reference guide and invariably need frequent updating. Professional discretion and consultation with other appropriate resources are recommended for clinical decision-making purposes: for example, see http://QTDrugs.org for updated listings of drugs influencing LQTS/TdP, and http://drug-interactions.com for agents that are P450-enzyme substrates, inhibitors, or inducers.

Cardiac-Risk Screening

All persons entering MMT should have a medical examination that includes an assessment of cardiac health, and this information should be periodically updated. Relevant information can be gathered from a history-taking, physical examination, routine laboratory tests, and a screening 12-lead ECG in patients with established cardiovascular disease (Nabel 2000; O'Rourke et al. 2003). ***Table 2*** outlines key clinical factors to consider when assessing a patient's risk for developing LQTS and/or arrhythmia.

Table 2: Clinical Factors for Assessing Cardiac Arrhythmia Risk*

Family History (blood relatives)
Sudden or unexplained death at a young age (< age 50)

Patient History
Drug use (cocaine, amphetamines, alcohol, diuretics, etc., and OTC products [particularly ephedra])
Prescribed QT-prolonging or P450-inhibiting drugs
Congenital long QT syndrome (LQTS)
Known heart disease (particularly CAD or CHF)
Eating disorders (including bulimia and anorexia)

Laboratory Tests
Urine toxicology (showing proarrhythmic drugs, such as amphetamines or cocaine)
Depleted electrolytes (potassium, magnesium)

Recent Symptoms
Unexplained seizures
Exertional chest pain/discomfort
Exertional dyspnea (breathlessness)
Orthopnea (breathlessness on lying down)
Unexplained syncope (fainting) or unexplained near-syncope (dizzy, faint feeling)
Heart palpitations

Physical Examination
Abnormal pulse rate/rhythm
Jugular venous distension
Pulmonary rales (crackles)
Abnormal heart gallop

*This list focuses particularly on LQTS/arrhythmia, rather than overall cardiovascular health. CAD = coronary artery disease, CHF = congestive heart failure.
Sources: McMurray et al. 2000; Nabel 2000; O'Rourke et al. 2003

A carefully obtained patient history is the cornerstone of arrhythmia-risk screening and a guide for further examination or testing. Family history can be important because many cardiac disorders are hereditary (McMurray et al. 2000). Drug-use history (including currently used illicit and licit [prescription, OTC, herbal] substances) is of special importance, since many agents can interact with methadone to influence cardiac repolarization.

The cardinal symptoms of cardiovascular disease, some of which relate to arrhythmia, include: exertional chest discomfort, breathlessness (dyspnea), palpitations, syncope, and peripheral edema. However, these are nonspecific and do not definitely denote disease; many cardiac conditions can be asymptomatic (Nabel 2000; O'Rourke et al. 2003).

Identifying specific factors influencing the development of TdP is inherently challenging because it is a "moving target" (Priori 1998). For example, a patient may be at risk early in therapy or much later because of unreported or seemingly inconsequential circumstances, such as intervening illness (e.g., vomiting or diarrhea leading to hypokalemia) or the sporadic abuse of cardiotoxic substances (e.g., cocaine).

MMT Practice Implications

Sound medical practice dictates a need for continued vigilance to identify individual patient risk factors for cardiac arrhythmia. Ongoing assessments of heart health during MMT serve as an important preventative measure.

At present, it seems reasonable to consider that methadone – alone or, more commonly, in combination with other drugs and/or cardiac risk factors – may prolong the QT interval and potentially influence TdP in susceptible patients (Eap et al. 2002). Based on currently available evidence, and the commentary above, the following general recommendations might be noted:

- Adequate methadone doses are essential for therapeutic success, and it *does not* appear necessary to alter methadone dosing practices – such as, arbitrarily lowering doses – solely due to concerns about possible cardiac repolarization effects. *However*, in patients with multiple pre-existing risk factors for arrhythmia (Tables 1 and 2), screening ECGs may be a prudent component of major dose increases.
- Routine ECGs, incurring added expense and inconvenience, for *all* patients entering or continuing MMT are *not* recommended. Screening ECGs should be reserved for individual patients with established cardiovascular disease or those with clinically-significant arrhythmia-risk factors.
- If an ECG is deemed necessary, results should be reviewed by a physician with experience in measuring and interpreting waveforms, primarily the QT interval. When feasible, ECGs should be performed during peak drug concentrations.
- The use of methadone in patients already known to have significantly prolonged QT intervals has not been systematically studied and expert consultation (e.g., cardiologist, internist) might be sought in these and other cases in which there are specific concerns about cardiac complications during MMT (also see Table 3). However, this should not necessarily deter the appropriate use of methadone in these patients.

In conclusion, methadone remains an effective and well-tolerated therapy for the treatment of opioid addiction when prescribed appropriately. A sound understanding of its potential for QT-prolongation in the context of other arrhythmia risk factors will allow clinicians to optimize safety during MMT. To help provide individualized patient assessments and treatment plans that preserve heart health, MMT staff may want to consider the clinical practice suggestions outlined in ***Table 3***.

Research in this area is ongoing and future refinements of these practices may be necessary. Meanwhile, the relatively small potential risk of adverse cardiac effects that have been reported with methadone should be weighed against the more serious risks of withholding MMT; including, a high likelihood of illicit drug use and its related morbidity, mortality, and public health ramifications.

Table 3: Suggestions for Optimizing Cardiac Safety During MMT*

- ☐ Patients entering MMT should be screened for cardiac risk factors and medical records for all patients should be periodically updated.
- ☐ Records should note prior and current cardiac problems, family history of cardiac conditions, past and present substances abused (including tobacco), and current medications (including OTC and herbal products). *See Tables 1-2.*
- ☐ A 12-lead ECG might be considered in…
  - new patients with a history of arrhythmia or prolonged QTc, a family history of premature sudden death, and/or other significant arrhythmia risk factors;
  - ongoing MMT patients suspected of having arrhythmia risks, and especially before starting QT-prolonging medications or methadone metabolism inhibitors in those patients.
- ☐ A followup ECG should be performed in such patients to detect significant changes from baseline.
- ☐ Patients with QTc prolongation during MMT should be evaluated for modifiable risk factors, such as concomitant medications that affect cardiac repolarization, inhibit methadone metabolism, or are known to cause electrolyte imbalance, etc.
- ☐ Consultation with experts and/or closer monitoring might be considered in patients with…
  - known or detected conditions affecting heart rhythm (such as, CHF with reduced ventricular function);
  - unexplained syncope or seizures;
  - QTc > 460 msec (in males or females);
  - significant increase in QTc (>60 msec) from baseline;
- ☐ Patients at risk of arrhythmia should be educated on symptoms to watch for – e.g., "racing" heartbeat, dizziness, seizures, or fainting spells – and encouraged to contact the clinic immediately. Clinic staff should be trained in handling such calls from patients: e.g., appropriately encouraging those with severe symptoms to call 911, facilitating referrals to urgent care, or arranging for ECGs.

***NOTE:** None of these suggestions is intended to deter the use of methadone in any patient who would otherwise benefit from MMT.*

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