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INNOVATIVE TECHNIQUES

REVIEW ARTICLE

# QT Prolongation and Arrhythmia Risk in Methadone Maintenance Treatment

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**ABSTRACT.** *Methadone maintenance therapy (MMT) is the most widely prescribed and most effective treatment for opioid dependence. Methadone is a long-acting synthetic opioid that is a potent blocker of the delayed rectifier potassium ion channel, which may result in QT interval prolongation (QTP) and increased risk of torsades de pointes (TdP) in susceptible individuals. MMT-associated TdP is rare; however, its gravity has prompted a re-examination of the risks and benefits of MMT. This article reviews the current understanding of the benefits and the arrhythmia risk of MMT and presents a perspective on current primary and secondary prevention strategies, including advances that may alter future management.*

**KEYWORDS.** *methadone, QT, ECG screening, torsades de pointes, buprenorphine.*

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## Introduction

Methadone, a long-acting synthetic opioid that prevents or reverses withdrawal symptoms and blocks the euphoric effects of other opiates, is the most widely used therapy for opioid dependence. Methadone induces prolongation of the rate-corrected QT interval (QTc) through blockade of the rapidly activating delayed rectifier potassium current (IKr) through the cardiac human ether-a-go-go-related gene (hERG) channel. Both the degree of QTc prolongation associated with methadone and the efficacy of methadone in opioid dependence increase with higher doses of methadone, resulting in a safety–efficacy paradox.[1]

The benefits of methadone maintenance therapy (MMT) include decreased mortality, decreased criminal activity, and greater adherence to treatment than drug-free alternative treatment.[2] MMT is also associated with reduced transmission of HIV and viral hepatitis.[2] These benefits of MMT must be weighed against the increasingly well-documented risk of methadone-induced QT interval prolongation (QTP) and associated torsades de pointes (TdP).[3,4] Absence of a suitable alternative to MMT, particularly in patients requiring high doses, makes management of patients with QTP uniquely challenging. Further, although ventricular arrhythmias are rare, even in the setting of significant QTP, they are potentially life threatening. Predisposing risk factors for arrhythmia in the setting of drug-induced QTP are well established.[5]

## Risk factors for ventricular arrhythmias

Various thresholds for QTc prolongation have been proposed; however, a QTc interval >500 ms is an accepted threshold for increased arrhythmia risk. QTP >500 ms has been reported in 1.3–16% of MMT patients in various cohorts and is rarely associated with methadone doses less than 100 mg/day.[1,4] Although most sudden cardiac arrests on MMT have been reported at high doses, life-threatening arrhythmias have been described at dosages as low as 29 mg/day.[4] Although the precise incidence remains undetermined, arrhythmia risk increases with degree of QTP.[5] Yet, ventricular arrhythmias remain rare even with QTP >500 ms. The risk of drug-induced ventricular arrhythmia is modulated by clearly identified predisposing factors including hypokalemia, structural heart disease, hepatic cytochrome P450 inhibitors, and genetic predisposition.[6] At least one of these risk factors

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was present in the majority of documented cases of ventricular arrhythmias in MMT patients.[4,7,8]

A baseline electrocardiogram (ECG) will not identify all patients with susceptibility to drug-induced QTP. Decreased repolarization reserve, as seen in both manifest and subclinical congenital long QT syndrome (LQTS), is the underlying pathophysiology of genetic susceptibility to drug-induced QTP. Cardiac repolarization is determined by net outward current over time, resulting from the sum of inward and outward currents during the plateau of the action potential. A defect in any one of these currents may therefore remain subclinical without ECG abnormality if other pathways to normal repolarization are intact and able to compensate. A subclinical genetic defect in a single ion channel responsible for repolarization, as may be seen in a patient with the gene for congenital LQTS but normal QT interval on ECG, may consequently result in pronounced QTP with administration of a hERG-blocking medication like methadone. Prolongation of action potential duration contributes to the formation of early after-depolarizations (EADs) and increased heterogeneity of myocardial repolarization, which facilitate the onset of ventricular arrhythmias.

## Proposed guidelines

Guidelines for ECG ''screening'' in MMT patients have been proposed as a mechanism for detecting MMT-associated QTP and TdP risk.[9] These guidelines have not been validated in a clinical population and have not been widely accepted. Screening ECG to detect arrhythmia risk in an MMT population is limited by a number of factors. First, the majority of patients who have developed ventricular arrhythmias associated with MMT have baseline normal QTc and normal QTc upon withdrawal of methadone. Thus, it is unlikely that a baseline ECG will correctly identify patients at high risk of future events. Moreover, there is significant risk of ''false positives'' and the consequent potential erroneous determination that persons for whom the myriad benefits of MMT have been established would not receive treatment. Finally, the cost-effectiveness of a screening program is uncertain when considering the cost of the ECG itself as well as the cost of the echocardiogram and/or exercise stress tests that will be required for the 10–27% of patients with ECG abnormalities related and unrelated to QTc.[10] Resources may be better spent on education regarding identification and management of risk factors for ventricular arrhythmias in MMT patients. A more efficient and effective approach is focused ECG in MMT patients with additional risk factors or signs/symptoms suggestive of ventricular arrhythmia.[11]

## Secondary prevention

Management of MMT patients with prolonged QTc interval without manifest ventricular arrhythmia requires careful consideration of risks and benefits of continuing MMT or altering therapy. In any case, more frequent monitoring, counseling about worrisome symptoms and elimination of contributing factors such as additional QTc-prolonging medications and electrolyte abnormalities are required. It is our practice to use potassium-sparing diuretics to maintain normokalemia in patients at risk.

The initial management of a MMT patient presenting with QTP and polymorphic ventricular ectopy or TdP includes magnesium supplementation, isoproterenol and temporary pacing if arrhythmia persists. Once the patient is stabilized and reversible risk factors for QTP have been addressed, a plan for ongoing maintenance therapy must be established. A number of approaches have been suggested for the secondary prevention of ventricular arrhythmias in MMT patients. Buprenorphine, a synthetic opioid approved for substance abuse treatment, is an effective alternative for patients who do not require high-dose methadone.[12] Buprenorphine has not been associated with QTc interval prolongation or ventricular arrhythmias.[3] Buprenorphine's ratio of the 50% *in vitro* inhibitory concentration of IKr to maximal serum concentration, a strong predictor of arrhythmia risk, is an order of magnitude lower than that of methadone.[13] There are practical limitations to expanded buprenorphine use, including restricted access and cost. Nevertheless, buprenorphine therapy should be attempted in patients who manifest ventricular arrhythmias on MMT. We have previously proposed a strategy for successful transition from methadone to buprenorphine.[14]

Implantable cardioverter-defibrillators (ICDs) have been suggested for MMT patients with symptomatic ventricular arrhythmias. While ICDs effectively prevent sudden death in these patients, the relatively high procedure-related complications and recurrent shocks in this group are cause for concern.[15] Regardless, in patients with ICDs, aggressive management of arrhythmia risk factors remains vital to minimize ICD shocks.

Methadone is currently administered in the United States as a chiral mixture of (R,S)-methadone, although (R)-methadone is a 10-fold more potent $\mu$-opioid receptor agonist,[16] and a 50-fold more potent analgesic[17] than (S)-methadone. In addition, *in vitro* data have demonstrated stereoselectivity block of hERG channel by (S)-methadone, which is 3.5 times more potent than (R)-methadone.[18] Additionally, slow metabolizers of methadone, the 6% of the white population with deficiency in CYP2B6, have elevated levels of (S)-methadone, but not of (R)-methadone due to the stereoselectivity of the enzyme.[19] Thus, (R)-methadone is primarily responsible for the therapeutic benefit of methadone in MMT, while (S)-methadone is primarily responsible for the methadone-associated risk of QTP. A recent study in which (R,S)-methadone was briefly substituted for half-dose (R)-methadone in 39 MMT patients showed decreased QTc interval for (R)-methadone without decrease in efficacy.[20] (R)-methadone is currently available only in Germany, but if these findings are confirmed, (R)-methadone would be an appealing alternative to (R,S)-methadone, particularly for MMT patients at risk for ventricular arrhythmia.

## Conclusion

Despite the relatively high prevalence of QTP in MMT patients, ventricular arrhythmia and sudden death are rare, estimated conservatively to be 0.06 per 100 patient years.[21] Nevertheless, recently reported series of QTP and ventricular arrhythmias have prompted a re-examination of the risks and benefits of MMT and focused greater attention on both primary and secondary prevention of ventricular arrhythmias in MMT patients. Currently, evidence does not support a strategy of routine ECG screening. The optimal management of asymptomatic MMT patients with QTP is unclear, and whether withholding MMT in such patients will reduce incidence of sudden death is uncertain. In fact, it is equally possible that withholding MMT will lead to opiate relapse with its associated consequences. Given the extensive evidence of the benefits of MMT, any decision to withhold MMT should be made cautiously. Rather than ECG screening, resources are better spent on education and ongoing clinical assessment of risk factors that are easily identified and more predictive of arrhythmia risk than widespread ECG screening. In MMT patients who develop ventricular arrhythmias, transition to buprenorphine should be considered and risk factors for arrhythmia should be managed aggressively. Although currently unavailable in the United States, (R)-methadone is a promising therapy that may prove a safe therapeutic alternative to the currently available racemic methadone.

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