

QTc Interval Screening in Methadone Treatment

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Description: An independent panel developed cardiac safety recommendations for physicians prescribing methadone.

Methods: Expert panel members reviewed and discussed the following sources regarding methadone: pertinent English-language literature identified from MEDLINE and EMBASE searches (1966 to June 2008), national substance abuse guidelines from the United States and other countries, information from regulatory authorities, and physician awareness of adverse cardiac effects.

Recommendation 1 (Disclosure): Clinicians should inform patients of arrhythmia risk when they prescribe methadone.

Recommendation 2 (Clinical History): Clinicians should ask patients about any history of structural heart disease, arrhythmia, and syncope.

Recommendation 3 (Screening): Obtain a pretreatment electrocardiogram for all patients to measure the QTc interval and a

follow-up electrocardiogram within 30 days and annually. Additional electrocardiography is recommended if the methadone dosage exceeds 100 mg/d or if patients have unexplained syncope or seizures.

Recommendation 4 (Risk Stratification): If the QTc interval is greater than 450 ms but less than 500 ms, discuss the potential risks and benefits with patients and monitor them more frequently. If the QTc interval exceeds 500 ms, consider discontinuing or reducing the methadone dose; eliminating contributing factors, such as drugs that promote hypokalemia; or using an alternative therapy.

Recommendation 5 (Drug Interactions): Clinicians should be aware of interactions between methadone and other drugs that possess QT interval–prolonging properties or slow the elimination of methadone.

Ann Intern Med. 2009;150:387-395.

www.annals.org

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This article was published at www.annals.org on 20 January 2009.

Editor's Note: Some members of an expert panel proposed the recommendations presented in this publication. Two panel members declined acknowledgment for the publication. This publication is not a federal guideline. A government agency has recently forwarded draft recommendations related to QTc interval screening in methadone treatment for field review prior to finalization.

Methadone, the most widely used agent for opioid maintenance, may prolong the rate-corrected QT interval (QTc) and result in torsade de pointes (1). This association recently came into focus when the U.S. Food and Drug Administration (FDA) issued a physician safety alert regarding increasing deaths and cardiac arrhythmias (2), which was followed by a manufacturer's black box warning (3). The methadone derivative levacetylmethadol also prolongs the QTc interval; its use requires performance of pretreatment electrocardiography (ECG), and it is no longer actively marketed (4).

Prolongation of the QTc interval is the mandatory substrate for development of torsade de pointes and is the most commonly scrutinized pharmacologic adverse effect evaluated during new drug development and postmarketing surveillance (5, 6). Drug-induced arrhythmia often results from multiple factors, including hypokalemia; structural heart disease; hepatic cytochrome P450 inhibitors; and genetic predisposition, manifested by a prolonged QTc interval at baseline (7). In a meta-analysis of 1288 patients who received the QT interval–prolonging drug sotalol, an increased pretreatment QTc interval was the strongest predictor of arrhythmia (mean QTc interval of 455 ms in those experiencing torsade de pointes versus 428

ms), which occurred in 2% of the overall cohort (8). A study of the antiarrhythmic drug dofetilide found a 2-fold increased risk for sudden death if the pretreatment QTc interval exceeded the upper quartile value of 479 ms, highlighting the importance of pretreatment ECG screening for identifying susceptible patients (9).

Although many drugs prolong the QTc interval, torsade de pointes is associated with fewer drugs and is often accompanied by predisposing risk factors (10), including bradycardia (11, 12). Women have a slightly longer QTc interval than men and are at greater risk for arrhythmia (13). Proposed thresholds for QTc interval prolongation have been set as low as 430 ms for men and as high as 470 ms for women (14–16). Despite these varying definitions, the international regulatory guidance for drug development suggests a sex-independent categorical threshold for QTc interval prolongation of 450 ms (6). A QTc interval greater than 500 ms is an accepted threshold for significant arrhythmia risk (17). The paucity of long-term studies of

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QTc interval—prolonging drugs in large populations makes it difficult to assign a relative risk for arrhythmia, although a QTc interval greater than 500 ms was associated with a 4-fold increase in syncope or sudden death, presumably from torsade de pointes, in patients with congenital long QT syndrome (18). Limitations of QTc interval screening include selecting a rate-correction formula at extremes of heart rate, choosing between manual or automated measures, and the limited predictive value for arrhythmia risk at the individual level. Despite these limitations, QTc interval screening is the current standard for assessing drug safety in all domains of medicine: clinical practice, drug development, and regulatory assessment for drug withdrawal or manufacturers' labeling changes (19).

Against this background, an expert panel was convened to address the cardiac effects of methadone. (For a list of acknowledged members of the expert panel, see the Appendix, available at www.annals.org.) Because fewer than half of the physicians surveyed among accredited opioid treatment programs in the United States were aware of the association between methadone and QTc interval prolongation (20), the panel believed a consensus document was warranted. The objectives were to synthesize available evidence regarding methadone's proarrhythmic effects and formulate a clinical practice guideline, while being mindful that methadone is a niche medication with few therapeutic alternatives (21) and is associated with a substantial reduction in mortality among treated versus untreated heroin addicts (22).

METHODS

Expert Panel

In May 2003, the Center for Substance Abuse Treatment (CSAT) of the Substance Abuse and Mental Health Services Administration convened a meeting, "National Assessment of Methadone-Associated Mortality," where preliminary evidence suggesting the proarrhythmic properties of methadone was presented (23). This meeting reconvened on 20 July 2007 as "Methadone Mortality—A Reassessment" (24). One recommendation that emerged was the formation of a multidisciplinary expert panel on the cardiac effects of methadone. This panel included electrophysiologists, pain-management specialists, and epidemiologists. Representatives from the FDA, the National Institute on Drug Abuse, the American Association for the Treatment of Opioid Dependence, and the American Society of Addiction Medicine were also present.

The panel met on 19 and 20 December 2007 and reviewed selected articles solicited from members before the meeting. All members disclosed any conflicts of interest. We used a standard consensus decision-making approach that was inclusive (all key stakeholders were invited), participatory, and solution-oriented. Specifically, we collectively established the need for a clinical practice guideline regarding cardiac safety. We then drafted guide-

line recommendations that were iteratively modified and agreed to on the second day. The committee chair selected a writing group to perform a more in-depth literature review and craft a guidance document. This manuscript was circulated in advance of a second expert panel meeting on 15 and 16 July 2008, at which time, participating members reviewed, refined, and then approved the recommendations, which were sent to CSAT.

Literature Review

Two reviewers from the writing group with expertise in cardiology and electrophysiology independently searched MEDLINE and EMBASE (1966 to June 2008) to identify publications that addressed the cardiac effects of oral and intravenous methadone. We limited our searches to English-language articles but not to humans. We reviewed these articles along with mortality data retrieved from the aforementioned meetings of the CSAT, national opioid treatment guidelines from the United States and other countries, and background articles on QTc interval prolongation (Figure). We did not prespecify critical appraisal criteria, although we paid particular attention to larger clinical studies in terms of validity and relevance. We sorted literature according to the following topical or study design categories: experimental (in vitro) data, clinical case series of QT interval prolongation or torsade de pointes related to methadone, forensic series, cross-sectional investigations, and prospective cohort studies or randomized trials. When available, we extracted information regarding the relationship between methadone dose and cardiac repolarization. Finally, 2 reviewers independently evaluated the association between methadone and both QTc interval prolongation and torsade de pointes by adapting a quantitative method for estimating the probability of adverse drug reactions (25) to assess whether the likelihood of direct causation was definite, probable, possible, or doubtful.

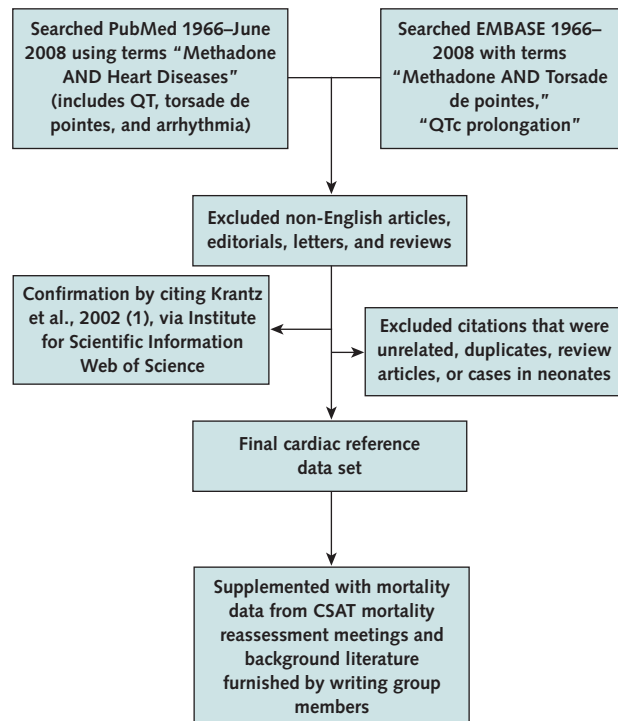
Role of the Funding Source

The CSAT of the Substance Abuse and Mental Health Services Administration sponsored the 2 expert panel meetings. It had no role in the design, data collection, analysis, or manuscript preparation. Moreover, the views presented in this document are those of the authors and other referenced sources. They do not necessarily reflect the views or policies of the Department of Defense, the CSAT, the Substance Abuse and Mental Health Services Administration, or any other part of the U.S. Department of Health and Human Services.

EVIDENCE LINKING METHADONE WITH QTc INTERVAL PROLONGATION AND TORSADE DE POINTES

We evaluated published data on the relationship between oral and intravenous methadone hydrochloride and

Figure. Study flow diagram.



CSAT = Center for Substance Abuse and Treatment; QTc = rate-corrected QT interval.

QTc interval prolongation and torsade de pointes. A summary of that evidence follows.

Experimental

The most common mechanism of drug-induced QT prolongation and torsade de pointes is blockade of the human cardiac ether à go-go–related gene (hERG), which encodes I_{kr} , the delayed-rectifier potassium ion current (26). Blockade of this cardiac ion channel prolongs the terminal portion of the cardiac action potential and causes delayed repolarization, which manifests as QTc interval prolongation on the surface ECG. Methadone has been shown to be a potent inhibitor of the hERG channel, capable of achieving 50% in vitro inhibitory concentration of I_{kr} at approximately 1 to 10 μM (27). The ratio of the 50% in vitro inhibitory concentration of I_{kr} to maximal serum concentration, a strong predictor of arrhythmia risk, is identical for methadone and levacetylmethadol and an order of magnitude more potent than buprenorphine, another synthetic opioid approved for substance-abuse treatment. Kornick and colleagues (28) observed that intravenous methadone is associated with greater QTc interval prolongation than the oral preparation. This formulation, which contains 0.5% chlorobutanol as a preservative, resulted in a mean increase in QTc interval from baseline of 41.7 ms (SD, 7.8). The investigators also performed an in vitro study that demonstrated that chlorobutanol potenti-

ated the impact of methadone on hERG channel blockade, which may account for the magnitude of the intravenous formulation's effect on repolarization (28).

de Vos and colleagues (29) reported peak plasma methadone levels in the μM range, which would overlap with concentrations that produce hERG channel blockade in vitro. A priori prediction of QTc interval effects are problematic because of interindividual variability in serum levels for any given dose due to differences in hepatic clearance (30). Specifically, methadone is metabolized by the cytochrome P450 system, and inhibitors of this enzyme can markedly increase plasma area-under-curve measurements (31). In addition, 2% of the population have unsuspected polymorphisms in the hERG channel gene that may be associated with increased sensitivity to hERG channel blockade by methadone or similar compounds (32).

Beyond its effect on cardiac repolarization via blockade of hERG channels, methadone has additional properties that may predispose to development of torsade de pointes. Risk for torsade de pointes is enhanced in the setting of bradycardia, and methadone seems to exhibit negative chronotropic effects through 2 key mechanisms: calcium-channel antagonism (33, 34) and anticholinesterase properties (35–37). This in vitro potential for bradycardia has been confirmed clinically (38–40).

Clinical Case Series

In 1973, a series of patients addicted to heroin was evaluated for predisposing risk factors for sudden cardiac death (41). The investigators observed QTc interval prolongation more commonly among persons with urine toxicology documenting the presence of methadone. However, no scientific evidence had established that methadone possessed cardiac toxicity, and analysis was limited by the presence of multiple drugs of abuse in the patients. It was not until almost 30 years later that a study of a North American series of 17 patients (1) found an association between very high doses of methadone and torsade de pointes. Since then, a growing body of evidence (42–63) has demonstrated an association between methadone and QTc interval prolongation and torsade de pointes. Evaluation of these cases suggests that many occurred in the setting of additional contributing factors and were often associated with relatively high doses of methadone.

The largest series to date was derived from a search of the FDA MedWatch system, which identified 59 cases of QTc interval prolongation or torsade de pointes associated with methadone (64). Eight percent were fatal, and most involved dosages of methadone exceeding 100 mg/d. Because only a fraction of drug-related serious adverse events are voluntarily reported to FDA MedWatch (65), the number of arrhythmia episodes attributable to methadone may be substantially higher. A more recent series described 8 patients receiving methadone maintenance therapy who presented with aborted sudden death or torsade de pointes and required implantable cardioverter–defibrillator place-

ment (66). Patients were receiving high doses of methadone (mean, 204 mg/d [SD, 173]) and were followed longitudinally for a mean of 27 months. Six of 8 patients continued methadone therapy; 1 died and 3 others received shocks for recurrent torsade de pointes. This suggests that patients who experience overt torsade de pointes are at substantial risk for recurrent arrhythmia if methadone therapy is continued.

Forensic Series

In addition to the clinical case series that link methadone with arrhythmia, a growing number of medical examiner investigations (67–70) report unexplained methadone-associated deaths. Although it is prescribed much less frequently than other opioids, methadone seems to be disproportionately involved in opioid-related deaths (71). Deaths associated with methadone in these autopsy series have increased over time and have occurred in multiple geographic regions, thereby providing insight into the scope and extent of the problem. However, given the inherent limitations of autopsy data, these series cannot distinguish the cause of death as arrhythmic or attributable to respiratory depression from overdose.

Information has recently emerged on a possible link between the increasing incidence of sudden death associated with methadone and its proarrhythmic properties. Chugh and colleagues (72) found 72 cases of sudden death over 4 years in which methadone was detectable in serum and another 106 cases in which it was not. A detailed cardiac autopsy was performed in 22 patients with therapeutic methadone levels of 0.1 to 0.9 mg/L, of whom only 23% had evidence of structural heart disease. By contrast, most (60%) patients who had sudden death without detectable methadone had structural heart disease. Sudden death in the absence of detectable cardiac disease is often attributable to a catastrophic arrhythmia. The critical implication of this study is that methadone is associated with sudden cardiac death even after elimination of obvious overdose deaths. It should be emphasized that this study is only inferential, although its findings are consistent with methadone's potent proarrhythmic effects *in vitro*, the large number of reported cases of torsade de pointes, and the likelihood that a small proportion of arrhythmic events will be fatal (73, 74).

Cross-sectional Data

We found cross-sectional studies comprising 4 ambulatory cohorts and 1 inpatient cohort. An analysis of 83 patients receiving methadone maintenance therapy in Italy (75) noted that most (83%) had a baseline QTc interval that exceeded the population-expected value based on age and sex; 2 patients had a QTc interval that exceeded 500 ms. A larger cross-sectional study of 138 patients by Peles and colleagues (76) observed that 16% had QTc interval prolongation, defined as greater than 450 ms. All patients with prolonged QTc interval were receiving methadone dosages exceeding 120 mg/d. Three (2%) patients had a

QTc interval that exceeded 500 ms. Over 2 years of follow-up, 2 patients died, both of whom had a QTc interval greater than 500 ms. Ehret and colleagues (77) retrospectively analyzed 247 hospitalized patients with a history of intravenous drug use, including 167 patients receiving long-term methadone therapy. The investigators found marked QTc prolongation (defined as >500 ms) among 16% of patients who received methadone. In contrast, no QTc interval measurement exceeded 500 ms among the 80 intravenous drug users not receiving methadone. Factors predicting QTc interval prolongation according to multivariate regression analysis included hypokalemia, liver disease, and concomitant use of hepatic cytochrome P450 inhibitors.

The largest cross-sectional comparative study to date (78) analyzed 393 patients receiving methadone and 43 patients receiving buprenorphine maintenance therapy in Copenhagen, Denmark. The investigators observed QTc interval prolongation (>440 ms) among 32% of patients who received methadone, whereas no patient who received buprenorphine had QTc interval prolongation. Similar to Peles and colleagues' findings, 8 (2%) patients who received methadone had a QTc interval greater than 500 ms and all were receiving more than 100 mg/d. Similar findings were also documented in a cohort of 104 patients with chronic pain (79) receiving methadone; 33% had QTc interval prolongation, defined as greater than 430 ms in men and 450 ms in women.

Prospective and Randomized Trial Data

One small study (80) noted a mean increase in QTc interval of 20 ms on initiation of methadone treatment. In the largest prospective cohort study to date, Martell and colleagues (81) evaluated 167 new entrants into methadone maintenance therapy. The investigator who interpreted ECGs was blinded to dose and time interval. Oral methadone induction resulted in a statistically significant increase in the mean QTc interval of 12.4 ms (SD, 23) at 6 months, which persisted at 12 months. Krantz and colleagues (82) observed a similar increase in QT interval dispersion (9.5 ms [SD, 18.6]), a marker of heterogeneous cardiac repolarization, from baseline to 6 months among the study cohort. Two percent of patients exceeded a QTc threshold of 500 ms at 6 and 12 months.

Wedam and colleagues (83) reported ECG safety data from a prospective randomized trial that compared the effect of levacetylmethadol, methadone, and buprenorphine on the QTc interval. They observed QTc interval prolongation in 23% of patients who received methadone with a normal QTc interval at baseline. They conservatively defined QTc prolongation as greater than 470 ms in men and 490 ms in women. Of note, 10% of participants had a QTc interval that exceeded 500 ms during the study. In addition, the investigators observed progressive QTc interval prolongation from baseline at 4, 8, and 16 weeks.

Dose Effects on Cardiac Repolarization

As with most QT interval–prolonging drugs, the effects of methadone on cardiac repolarization are dose-dependent and evident in case reports as well as cross-sectional and prospective studies. Methadone dosages exceeding 100 mg/d have frequently been noted in published cases of torsade de pointes, and some case reports (43, 47, 55) highlight QTc-interval normalization after methadone discontinuation or dose reduction. Furthermore, many studies, including those of oral and intravenous methadone, demonstrate a positive correlation between dose and delayed cardiac repolarization (28, 75–79, 81, 84) among both addiction treatment and pain management cohorts. In Peles and colleagues' study (76), the correlation achieved statistical significance in the subset of patients abusing cocaine, which is consistent with a synergistic effect of methadone and cocaine on hERG channel blockade (85). In Fanoë and colleagues' study (78), the QTc interval increased by 10 ms for every 50-mg increase in methadone dose, which corresponded to a higher risk for syncope (odds ratio, 1.2 [CI, 1.1 to 1.4]).

With regard to serum levels, Martell and colleagues (81) prospectively demonstrated that the increase in QTc interval from baseline to 12 months after methadone initiation correlated with both trough and peak serum concentrations. Huber and colleagues (86) observed similar relationships with the methadone derivative levacetylmethadol. Taken in aggregate, the available literature supports a dose-dependent effect of methadone and levacetylmethadol on cardiac repolarization (Appendix Table, available at

www.annals.org). This creates a safety–efficacy paradox, because higher doses of methadone may reduce illicit opioid use (or diminish chronic pain) yet place patients at greater arrhythmia risk (87). It is important for clinicians to recognize that sudden cardiac death associated with methadone has been described at dosages as low as 29 mg/d, which suggests that arrhythmia can occur across a wide therapeutic range that includes dosages commonly used in both chronic pain and addiction treatment (64). This in turn suggests that methadone dosage is just one consideration with regard to limiting arrhythmia risk.

EXPERT PANEL RECOMMENDATIONS

We judged that available evidence definitely suggests that both oral and intravenous methadone hydrochloride cause QTc interval prolongation and torsade de pointes (Table 1).

We then deliberated and arrived at 5 recommendations for physicians prescribing methadone (Table 2). We concluded that arrhythmia risk associated with methadone is a direct consequence of its effect on cardiac repolarization. Hence, our recommendations are applicable to patients either receiving current treatment with methadone or being considered for initiation of methadone treatment for addiction or pain management. Electrocardiographic screening may also be performed on an individual basis in patients receiving methadone with multiple risk factors for QTc prolongation, including a family history of the long QT syndrome or early sudden cardiac death or electrolyte depletion, and on initiation of therapy with a cytochrome P450 inhibitor or other

Table 1. Probability Score for the Association of Methadone with QT Prolongation and Torsade de Pointes*

Question	QT Prolongation		Torsade de Pointes	
	Answer	Score	Answer	Score
Are there previous conclusive reports on this reaction?	Yes†	1	Yes‡	1
Did the adverse event occur after administration of the drug?	Yes†	2	Yes‡	2
Did the adverse reaction improve when the drug was discontinued?	Yes§	1	Yes	1
Did the adverse reaction reappear when the drug was readministered?	Yes¶	2	Yes¶	2
Are there alternative causes (other than the drug) that could on their own have caused the reaction?	No**	2	No††	2
Did the reaction reappear when a placebo was given?	Don't know	0	Don't know	0
Was the drug detected in the blood in concentrations known to be toxic?	Yes‡‡	1	Don't know	0
Was the reaction more severe when the drug was increased or less severe when the dose was decreased?	Yes§§	1	Don't know	0
Did the patient have a similar reaction when exposed to the same or similar drug previously?	Yes	1	Yes¶¶	1
Was the adverse event confirmed by any objective evidence?	Yes†	1	Yes‡	1
Total¶¶¶		12/13		10/13

* Adapted from reference 25 with permission of *Clinical Pharmacology & Therapeutics*.

† References 28, 43–45, 47–50, 52, 53, 57, 58, 62–64, 66, 75–79, 81–84, 95.

‡ References 43–45, 47, 48, 50, 52, 53, 57, 62–64, 66, 77.

§ References 43, 45, 47, 52, 55.

¶ References 43, 45, 47, 52.

¶¶ Reference 66.

** References 47, 66, 83.

†† References 47, 66.

‡‡ References 76, 81.

§§ References 28, 75–79, 84.

||| References 58, 66.

¶¶¶ A score ≥9 indicates a definite association, 5–8 a probable association, 1–4 a possible association, and 0 a doubtful association.

Table 2. Consensus Recommendations

- Recommendation 1 (Disclosure):** Clinicians should inform patients of arrhythmia risk when they prescribe methadone.
- Recommendation 2 (Clinical History):** Clinicians should ask patients about any history of structural heart disease, arrhythmia, and syncope.
- Recommendation 3 (Screening):** Obtain a pretreatment electrocardiogram for all patients to measure the QTc interval and then a follow-up electrocardiogram within 30 days and annually. Additional electrocardiography is recommended if the methadone dosage exceeds 100 mg/d or if patients have unexplained syncope or seizures.
- Recommendation 4 (Risk Stratification):** If the QTc interval is greater than 450 ms but less than 500 ms, discuss potential risks and benefits with patients and monitor them more frequently. If the QTc interval exceeds 500 ms, consider discontinuing or reducing the methadone dose; eliminating contributing factors, such as drugs that promote hypokalemia; or using an alternative therapy.
- Recommendation 5 (Drug Interactions):** Clinicians should be aware of interactions between methadone and other drugs that possess QT interval-prolonging properties or slow the elimination of methadone.

QTc = rate-corrected QT.

QTc interval–prolonging drug, including cocaine. Moreover, urgent evaluation that includes ECG screening is warranted for patients receiving methadone who have unexplained syncope or generalized seizures; if marked QTc interval prolongation is documented, torsade de pointes should be suspected. Panel recommendations are not intended to supplant clinical judgment or patient preferences and may not apply to patients with terminal, intractable cancer pain.

OTHER RECOMMENDATIONS AND GUIDELINES

Warnings about the proarrhythmic potential of methadone are catalogued in Thompson's MICROMEDEX (available at www.thomsonhc.com) and a Web site (10) that dynamically archives QTc interval–prolonging drugs. Although the revised product label for methadone suggests careful monitoring among patients with prolonged QTc intervals, it does not specify the form of monitoring. Thompson's MICROMEDEX is more declarative and advises ECG monitoring among patients with cardiac conduction abnormalities or those at increased risk; however, no definition of conduction abnormalities or the population at risk is provided.

The Medicines and Healthcare products Regulatory Agency in the United Kingdom highlights the risk for QT prolongation with methadone and recommends monitoring patients receiving high dosages (defined as >100 mg/d) but does not detail the monitoring approach (88). The United Kingdom guideline on clinical management of drug misuse and dependence incorporates this approach and suggests that patients be informed of the reasons for monitoring if screening is considered (89). The Canadian Methadone Maintenance Guideline is more specific and suggests performing ECG when methadone dosages exceed 150 mg/d and repeating ECG when the dosage approaches 180 to 200 mg/d (90). This guideline further proposes tapering the methadone dose and referring the patient to a

cardiologist if the QTc interval exceeds 470 ms. A recently published U.S. consensus guideline on parenteral methadone use in pain and palliative care (91), which principally focuses on inpatient therapy, recommends pretreatment ECG followed by repeated measurement after 24 hours and again after 4 days, when steady-state levels are achieved. This consensus document, however, provides no guidance on risk stratification or subsequent clinical actions on the basis of the measured QTc interval.

IMPLEMENTATION OF RECOMMENDATIONS

We acknowledge challenges in screening and arrhythmia risk stratification of patients. Identifying clinically relevant QTc interval prolongation remains difficult because of intraindividual temporal variability, different formulas for the QTc interval (such as the Bazett versus the Fridericia formula), and difficulty in defining the actual risk for arrhythmia that a prolonged QTc interval portends for any given individual. The QTc interval is most often calculated by using the Bazett formula (92): $QTc = QT \text{ interval (in ms) divided by the square root of the preceding RR interval (in seconds)}$. Although this formula is likely to overcorrect in the setting of high heart rates (6), it is nonetheless a reasonable method for screening purposes with the proviso that patients remain supine for approximately 5 minutes before ECG acquisition.

We discussed practical considerations for implementing our recommendation. First, to estimate the number of potential patients in opioid treatment programs who might be identified by QTc interval screening as being at very high risk for torsade de pointes ($QTc > 500 \text{ ms}$), we reviewed the 3 available ambulatory cohort studies that focused solely on opioid treatment programs (76, 78, 81). Of note, each documented an identical proportion of patients (2%) in whom the QTc interval exceeded 500 ms, although data from 1 randomized trial (83) suggested a higher proportion. Assuming that these 3 studies are representative of the population receiving methadone maintenance therapy in the United States, we project that approximately 5000 of the 250 000 patients in opioid treatment programs (93) would exceed this threshold and constitute the principal target for risk-reduction interventions.

Second, we discussed the question of automated versus manual interpretation of the QTc interval. Automated (computer-generated) measurements are more standardized and probably offer reasonable estimates of arrhythmia risk because most patients in opioid treatment programs do not have structural heart disease. In support of this, Martell and colleagues (81) prospectively evaluated both blinded manual readings performed by a cardiologist and automated readings and found essentially identical mean values for automated and blinded manual QTc measurements (418 ms [SD, 22] vs. 419 ms [SD, 23]; $r = 0.8$; $P < 0.001$). Another cross-sectional study (76) corroborated this finding: Blinded manual QTc readings performed by a

cardiologist were strongly correlated with the automated readings ($r = 0.997$, $P < 0.001$). Because these data were derived directly from opioid-dependent populations, we believe that practitioners may use automated readings as a screening tool for risk stratification. Practitioners who are uncertain about whether clinically significant QTc interval prolongation is present should repeat ECG or have the tracing interpreted by a cardiologist. Regardless, ECG screening for QTc interval prolongation does not require specialty care and has been judged appropriate in primary care settings (15). Therefore, we deem ECG screening with risk stratification feasible in opioid treatment programs and in the treatment of chronic pain in ambulatory and hospital settings.

SUMMARY

A large body of evidence suggests that oral and intravenous methadone is associated with QTc interval prolongation and torsade de pointes. Opioid treatment programs in the United States are accordingly challenged with integrating cardiac arrhythmia risk assessment into routine care process without reducing access to vital addiction treatment services. We believe that increased clinical vigilance will reduce sudden cardiac death among the approximately 250 000 patients receiving methadone in opioid treatment programs (93) as well as the nearly 720 000 patients receiving methadone for chronic pain through U.S. retail pharmacies (94). These recommendations may inform both the product labeling for methadone as well as practice standards for opioid treatment programs. Currently, among patients receiving methadone who develop marked QTc interval prolongation or torsade de pointes, clinicians have just 1 FDA-approved alternative therapy (buprenorphine). However, (R) methadone seems to exhibit less hERG-channel blockade than standard (R,S) methadone (95). Although currently unavailable in the United States, (R) methadone could prove to be a safe therapeutic alternative compared with the standard racemic mixture, pending larger prospective studies. Nonetheless, with regard to cardiac arrhythmia risk, standard methadone can be safely administered as long as the potential for QTc interval prolongation is recognized through ECG screening and appropriate clinical actions are taken in the presence of QTc interval prolongation.

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Note: Clinical practice guidelines/recommendations are intended to enhance patient care and do not supplant clinical judgment. This guideline, therefore, may not apply to all patients or clinical scenarios.

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or any other part of the U.S. Department of Health and Human Services.

Acknowledgment: The authors thank Sara Alan for administrative support, William Baker for manuscript review, and Laura Governale from the FDA Center for Drug Evaluation and Research Office of Surveillance and Epidemiology for assistance with data acquisition.

Potential Financial Conflicts of Interest: None disclosed.

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APPENDIX: CARDIAC EXPERT PANEL CONTRIBUTING MEMBERS

The following cardiac expert panel members are acknowledged*: Dr. Barry Stimmel (*Chair*), Dr. Mark Haigney, Dr. Margaret Kotz, Dr. Robert Rappaport, Dr. Mori Krantz, Dr. Frank Vocci, Dr. Judith Martin, Dr. Davendra Mehta, and Mr. Charles O’Keeffe.

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*Two panel members declined to be acknowledged.

Appendix Table. Dose-Dependent Effects of Methadone and Levacetylmethadol on the QTc Interval

Compound (Reference)	Variables Measured	Correlation	P Value
Oral methadone (81)	Serum trough concentration vs. change in QTc from baseline	0.37	0.008
Oral methadone (77)	Dose vs. absolute QTc	0.20	0.01
Oral methadone (84)	Dose vs. absolute QTc	0.51	0.03
Oral methadone (79)	Log-dose vs. absolute QTc*	0.60	0.01
Oral methadone (75)	Dose vs. absolute QTc	0.14	NS
Oral methadone (76)	Dose vs. absolute QTc	0.13	0.1
Oral methadone (78)	Dose vs. absolute QTc	0.28	<0.001
Intravenous methadone (28)	Log-dose vs. absolute QTc	NR	<0.001
Oral levacetylmethadol (86)	Dose vs. change in QTc from baseline	0.32	NR
Oral levacetylmethadol (86)	Serum trough concentration vs. change in QTc from baseline	0.47	NR

NR = not reported; NS = nonsignificant; QTc = rate-corrected QT.

* Male patients.