Comments and Response

Concerns About Consensus Guidelines for QTc Interval Screening in Methadone Treatment

TO THE EDITOR: The medical profession has been developing guidelines to improve opioid maintenance treatments for 40 years. The guidelines proposed by Krantz and colleagues (1) could set us back decades because they address only 1 extremely rare side effect with an unproven strategy of serial electrocardiography (ECG) on all patients regardless of risk.

Worse than that, Krantz and colleagues give no alternative clinical strategy to maintain treatment outcomes. Indeed, their current advice may even do the opposite if put into practice. Vague notions of avoiding methadone treatment or using lower doses would be as helpful as saying that patients with diabetes need to avoid insulin and, when unavoidable, should take only small doses. The only licensed alternative to methadone, buprenorphine, is simply not effective in a significant proportion of patients (2).

Justo and colleagues (3) reviewed the literature up to 2006 and found 40 cases of torsade de pointes in association with methadone treatment. None of the cases was fatal, and 85% were associated with a clear precipitant in addition to high-dose methadone treatment. Most patients with torsade de pointes have comorbidities or electrolyte disturbance contributing to their arrhythmia; therefore, ECG at a remote time could never prevent such cases.

Before recommending effective clinical guidelines, Krantz and colleagues should have gone back to the field and determined an incidence rate for tachycardia. They also need to propose a viable, safe alternative strategy to compare with guideline-based treatment in addiction clinics, which currently reduce the high mortality in the addiction population by approximately 75%.

Torsade de pointes rarely, if ever, occurs in young opioid-dependent patients starting methadone treatment. These guidelines should be taken along with a mountain of other clinical advice, and our patients should be treated individually, according to their needs. In the absence of other indications, patients prescribed methadone at more than 150 mg/d should probably be recommended routine ECG.

Andrew Byrne, MBBS
University of Sydney
Sydney, New South Wales 2006, Australia

Potential Financial Conflicts of Interest: Dr. Byrne owns a clinic that charges fees for dispensing buprenorphine and methadone in addiction treatment.

References

TO THE EDITOR: We read with great consternation the clinical guidelines by Krantz and colleagues (1) advocating rate-corrected QT interval (QTc) screening for methadone treatment. In our opinion, not only are the recommendations short-sighted and irresponsible, but they are also detrimental to society at large.

We foresee multidimensional problems with these guidelines. First, Krantz and colleagues do not appreciate that, for most opioid users (both former substance abusers and pain patients), methadone represents a last-resort treatment. Therefore, even if a prolonged QT interval is found, the likelihood that an equally effective alternative treatment could be implemented is remote (2).

Second, compared with the other potentially catastrophic risks associated with methadone, the chance of a fatal arrhythmia is minimal. The side effects and potential complications of opioid use in general far outweigh the marginally increased risk entailed by methadone use (3, 4). Not only methadone, but also oxycodone, has been associated with the surrogate outcome measure of a prolonged QT interval, suggesting that the full-fledged earthquake (that is, recommendations that in essence become restrictive practice mandates because of the litigious nature of our society) may be just over the horizon (5). Should we then perform serial ECG on every patient who initiates opioid therapy, including on emergency department visits and ambulatory surgical procedures? Or, because the sensitivity of 1 ECG screening is quite low, maybe we need to increase the surveillance interval to every month?

Finally, the guidelines do not address a possible relationship between changes observed on ECG and dose, dosing interval, and treatment duration. Does this imply that a patient taking methadone, 5 mg twice daily, should be treated identically to a patient taking 100 mg three times daily? If so, this would be antithetical to everything we’ve learned about drug-related toxicity.

We do agree that the surge in methadone use has resulted in a corresponding increase in drug-related deaths. But we have no way of knowing how many of these are due to arrhythmias, misuse, or lack of physician education. We do not live in a society in which time and resources are unlimited, people are altruistic, and cost is irrelevant. Besides cardiologists, the only people likely to benefit from the published recommendations are ECG manufacturers and trial lawyers.

Steven P. Cohen, MD
Johns Hopkins School of Medicine
Baltimore, MD 21205

Jianren Mao, MD, PhD
Massachusetts General Hospital, Harvard Medical School
Boston, MA 02114

Potential Financial Conflicts of Interest: Dr. Mao received grants from Takeda for a clinical study on neuropathic pain.

References
TO THE EDITOR: I am Chief Medical Director for Aegis Medical Systems’ network of 24 narcotic treatment programs throughout California. I am writing to share my serious reservations regarding the assertions made by Krantz and colleagues (1) in their recent guidelines.

Aegis has been serving California communities for more than 10 years and has been using methadone to safely treat more than 5000 patients on a daily basis. Aegis has not encountered any evidence of torsade de points attributable to our patients’ treatment with methadone. In fact, over more than 30 years (1969 to 2002), only 43 cases of methadone-associated torsade de points and 16 cases of QTc prolongation were reported to the U.S. Food and Drug Administration’s MedWatch program. In addition, other risk factors for QTc prolongation and torsade de points (for example, taking medications with known drug–drug interactions, low potassium or magnesium levels, and structural heart disease) were found in 75% of such cases.

Furthermore, in the case series (1) mentioned by Krantz and colleagues, approximately 82% (14 of 17) of those patients had known risk factors for arrhythmias, such as hypokalemia, or were concomitantly taking other drugs that could prolong the QTc interval. Therefore, Krantz and colleagues themselves cautioned that “[their] report should not be interpreted to suggest that high-dose methadone cannot be used safely.”

Both Aegis’ strict internal policies and state regulatory requirements dictate that Aegis physicians perform a thorough review of all patient deaths. Therefore, Aegis receives and reviews a coroner’s report in conjunction with each patient death. Aegis physicians are also in direct communication with the primary care physicians of their patients. Neither the communications concerning the care of thousands of patients nor the reviewed coroners’ reports have ever indicated any correlation between QTc prolongation and the treatment of our patients with methadone. Nonetheless, to effectively and reasonably address concerns raised by Krantz and colleagues, Aegis has updated its clinical risk management policy to require ECG for all patients entering methadone maintenance therapy. Cocaine has long been related to depression of heart rhythms, and alcohol has been shown to prolong QTc by up to 19%. In addition, many patients in methadone maintenance therapy are treated with multiple drugs that may alter electrical conduction in heart muscle tissue.

Fourth, past clinical investigations have shown minimal effects of methadone on QTc prolongation (3, 4). In a 2003 study of 50 pain patients (5), QTc intervals did not change during oral methadone therapy. Fifth, researchers have noted that 89% of plasma methadone is protein-bound, thereby possibly reducing the in vivo amount of methadone available to inhibit iHHERG to 11% (free fraction) and increasing the therapeutic index for methadone approximately 10-fold.

Sixth, laboratory studies are often based on methadone blood concentrations nearly 9 times greater than usual therapeutic levels recommended for patients on methadone maintenance therapy. In addition, past studies have been limited to cell cultures or animals, which do not necessarily translate to clinical effects on patients. Furthermore, in many case studies, high doses of methadone were applied directly to heart tissue on a single-dose basis. This is inconsistent with the actual long half-life of methadone and the steady blood serum levels common with methadone maintenance therapy.

Finally, effects on the heart’s electrical conduction are not always harmful. In fact, certain opioids (including methadone) have shown cardioprotective effects and have been important adjuncts in treating heart attacks and coronary artery disease (6, 7). The calcium-slowing effects of methadone may be analogous to the actions of certain heart medications that suppress some forms of arrhythmia (8). One study (9) found similarities between methadone and verapamil. Verapamil, a calcium-channel blocker used to treat hypertension and angina, has not appeared on any lists of agents known to prolong QTc or induce torsade de points; in fact, calcium-channel blocking may shorten the QTc interval.

Furthermore, Krantz and colleagues should have considered other effective measures to ensure the safety of patients, including education of patients on these concerns, collaboration with primary care physicians, and monitoring of patients with a history of cardiac conditions. Such measures would not have a detrimental effect on access to treatment.

Aegis believes that the medical diagnosis and the determination of a patient’s fitness for methadone treatment must be left in the hands of patients’ treating physicians. Aegis further believes that Krantz and colleagues neglected to consider the various medical, psychological, and cultural considerations that accompany drug addiction.

We would like to point out the following findings from previous studies and publications regarding the relationship between QTc prolongation and methadone. First, much of the evidence to date regarding QTc prolongation and methadone are the result of case reports and small case studies (1, 2). Second, many of these cases (82%) did not isolate methadone as the triggering element for QTc prolongation; rather, additional factors that could have played important roles in the diagnosis were not ruled out. QTc prolongation often results from a confluence of risk factors rather than a single causative agent.

Third, the prevalence of other substance abuse, such as cocaine, alcohol, and tobacco, would be expected in opioid-dependent persons entering methadone maintenance therapy. Cocaine has long been related to depression of heart rhythms, and alcohol has been shown to prolong QTc by up to 19%. In addition, many patients in methadone maintenance therapy are treated with multiple drugs that may alter electrical conduction in heart muscle tissue.

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Thus, some of methadone’s actions demonstrated in laboratory studies actually may provide a degree of cardiac protection in certain patients receiving methadone maintenance therapy. We hope that *Annals* will recognize these considerations and consider the complexity of this matter. Furthermore, we hope that *Annals* will present a more balanced view of these matters.

**George Girgis, MD**
Aegis Medical Systems
Agoura Hills, CA 91376

**Potential Financial Conflicts of Interest:** Chief Medical Director, Aegis Medical Systems; President, Nationwide Medical Group.

**References**


**TO THE EDITOR:** The clinical guidelines by Krantz and colleagues (1) raise important methodological concerns. Although Krantz and colleagues use a method for predicting adverse drug reactions, they neglect to use data extraction and quality assessment tools. In fact, they state that they “did not prespecify critical appraisal criteria.” This is contrary to *Annals’* “Information for Authors” (2), which requires guidelines to include a grading system, such as those described by the Conference on Guideline Standardization; the Grading of Recommendations Assessment, Development and Evaluation Working Group; or the U.S. Preventive Services Task Force (USPSTF).

On review of the 212 articles listed in *Annals’* online “Clinical Guidelines/Position Papers” collection (accessed 9 February 2009), I found 94 unique clinical guidelines. Excluding 2 updates on adult vaccination schedules, 54 of the remaining 92 guidelines used a grading system, whereas 28 guidelines systematically rated the quality of evidence supporting guideline recommendations. Eight of the 10 guidelines providing neither grade nor quality assessment were published before 1998, when such quality assessments became routine. Therefore, the guidelines by Krantz and colleagues are 1 of 2 guidelines published by *Annals* since 1998 that do not explicitly evaluate or grade the quality of evidence used in guideline recommendations. Using USPSTF criteria (3), the literature cited by Krantz and colleagues would result in a grade of I, indicating that the evidence is insufficient to determine the relationship between the benefits and harms of QTc screening. Had the authors expounded on this and incorporated recent methods (published in *Annals*) (4) for guidelines based on insufficient evidence, the reader would be better equipped to make rational clinical decisions.

Of further interest, although Krantz and colleagues summarize their recommendations in Table 2 under the title “Consensus Recommendations,” 2 of the panelists have declined acknowledgment in the publication, which raises the question: Was there consensus?

In addition, the online version (but not the print version) of this article states that 3 of the panel members have financial conflicts of interest related to support by Reckitt Benckiser (1 was formerly President and CEO), the producer of methadone’s main competitor (buprenorphine) in the treatment of opiate dependence. These disclosures were not made in the original, withdrawn version of the guidelines.

These issues call into question the quality of Krantz and colleagues’ recommendations, the independence of the authors, and the judgment of *Annals* in publishing clinical guidelines that fall well outside the normative standards.

**Gavin Bart, MD**
Hennepin County Medical Center
Minneapolis, MN 55415

**Potential Financial Conflicts of Interest:** Dr. Bart received a National Institutes of Health–National Institute on Drug Abuse Career Development Award to study the pharmacokinetics and pharmacogenetics of methadone.

**References**


**IN RESPONSE:** We appreciate the many thoughtful and provocative comments on our consensus guideline for QTc interval screening in methadone treatment. The common theme was a strong endorsement of methadone’s role as a cornerstone therapy in opioid addiction. Dr. Byrne and Drs. Cohen and Mao rightly assert that methadone may be a treatment of last resort with limited therapeutic alternatives. We agree and clearly acknowledge in our guideline that...
methadone is a niche medication (1) that must remain widely available despite the many alternative drugs for treatment of chronic pain and a second approved therapy, buprenorphine, in the addiction field. Indeed, our guideline does not mandate switching to an alternative therapy, even in the setting of marked (>500 ms) methadone-induced QTc prolongation. Instead, we suggest a measured approach of risk stratification that informs both a risk–benefit discussion as well as many individualized clinical actions to mitigate risk.

Dr. Girgis highlights the disproportionate increase in methadone-associated deaths in recent forensic studies (2). Specifically, he notes that coroners’ reports have not indicated a link between unexplained methadone-associated sudden death and the QTc interval. This is not surprising, because ECG data obtained before sudden cardiac death are rarely available to coroners. However, a recent autopsy cohort study by Chugh and colleagues (3) suggests that methadone-associated sudden deaths may have been the result of a fatal arrhythmia, because of the relative lack of structural heart disease in persons with modest serum methadone concentrations. Finally, Dr. Girgis cites the work of Lipski and colleagues (4) to suggest that methadone has minimal effect on the QTc interval. We respectfully disagree with this characterization, because 34% of methadone-treated patients in this study had significant QTc prolongation compared with only 18% of methadone-naive drug abusers.

We thank Dr. Bart for pointing out the inherent methodological limitations of our guideline. We acknowledge that the number and types of studies available regarding methadone cardiotoxicity are limited and do not lend themselves to critical appraisal criteria, meta-analytic techniques, or other quantitative quality assessments. Despite these inherent limitations, we adopted a validated clinical tool (5) to determine with certainty the link between methadone and torsade de pointes as a prerequisite to asserting the need for a risk mitigation strategy. Safeguarding patients from potentially fatal drug-induced arrhythmia creates a very different contextual framework than grading evidence for screening and treatment decision algorithms, such as the USPSTF guidelines that Dr. Bart alludes to. It is therefore no surprise that we found no evidence-based guideline recommendations from the USPSTF regarding mitigation of drug-induced torsade de pointes on review of the scientific literature (PubMed, accessed 10 May 2009). We are also unaware of any “effectiveness” evaluations of risk mitigation strategies that require ECG screening for drugs independently associated with torsade de pointes (6), including the methadone derivative levacetylmethadol (7). Finally, no scientific objections were raised to our recommendations during any of the cardiac expert panel meetings convened by the Center for Substance Abuse Treatment. Nonetheless, we respect the autonomy of clinicians to either change their views or decline acknowledgment. This in no way calls into question the integrity of the research process, the clinical science behind our guideline, or the editorial judgment in publishing it.

In conclusion, methadone is associated with a dramatic increase in deaths and cardiac arrhythmias. Arrhythmic events have often been associated with high doses of methadone or concurrent illicit drug use. Many patients in the addiction field fit into these categories, which underscores the importance of defining risk with ECG. We believe it is the increase in methadone deaths that imperils the future of methadone treatment rather than ECG monitoring, which is relatively simple, noninvasive, and inexpensive. The opioid treatment and pain management communities therefore must consider appropriate measures to address this challenge. Understanding the complex pharmacokinetic and pharmacodynamic properties of methadone (especially QTc prolongation) is an essential first step. Disclosure of arrhythmia risk to patients, ECG screening, and risk stratification that informs individualized treatment decisions are responsible next steps to ensure safety in this vulnerable population.

Mori J, Krantz, MD
Colorado Prevention Center
Denver, CO 80203

Judith Martin, MD
BAART Turk Street Clinic
San Francisco, CA 94102

Barry Stimmel, MD
Mount Sinai School of Medicine
New York, NY 10029-6500

Mark C.P. Haigney, MD
Uniformed Services University of the Health Sciences
Bethesda, MD 20814

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References
7. Product Discontinuation Notice: Orlaam (Levomethadyl hydrochloride acetate) Oral Solution, 10 mg/mL, CII. Columbus, OH: Roxane Laboratories; 23 August 2008.