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CSAT's QT Interval Screening in Methadone Report: Outrageous Fortune or Sea of Troubles?

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Awareness of sudden cardiac death (SCD) has increased over the past few decades, and there are ongoing efforts to develop risk stratification models that can identify susceptible individuals. Because survival of out-of-hospital cardiac arrest is less than 5%,[1] it is hoped that identification of risk factors for SCD will lead to prevention strategies.

In general, SCD may be caused by several different forms of arrhythmia, and ventricular tachycardia may be antecedent in as many as 25% of cases.[1] Ventricular tachycardia has many causes, including underlying cardiac disease, electrolyte abnormalities, inherited disorders of cardiac conduction, metabolic disorders, and drug/medication toxicity. It is, perhaps, incorrectly assumed that drug-related ventricular tachycardia and SCD are consistently preceded by prolongation of the electrocardiographic corrected QT (QTc) interval and that the QTc may, therefore, serve as a surrogate marker for the risk of developing ventricular tachycardia, torsade des pointes (TdP), or SCD.

It would be an outrageous fortune if simple screening for QTc prolongation provided positive predictive value for risk of SCD, but there are no prospective data to support its use in SCD risk stratification. Population cohort studies of SCD do not support the use of QTc interval as a surrogate risk marker. For example, the Framingham study found that 4.4% of adults had a QTc >440 msec and that there was no association between QTc and 25-year risk for total mortality, SCD, or cardiac related deaths.[2] A general population study in Denmark did find an association between a QTc of >440 msec and all cause and cardiac mortality.[3] However, this association disappeared after adjusting for known cardiac disease. A meta-analysis of studies (including the two abovementioned studies) following more than 36,000 participants concluded that there is no consistent evidence to support an association between QTc and increased mortality, except possibly in those with established cardiac disease.[4]

In the article “QT Interval Screening in Methadone Maintenance Treatment: Report of a CSAT Expert Panel” in this issue of JAD, Martin concludes that “An optimal strategy for identifying and reducing QT-associated risk has not yet been established.” In a contradictory statement, the next sentence reads, “Screening for risk is the current standard of care.” Herein begins a sea of troubles.

The panel makes four conclusions regarding clinical procedures. Two of these conclusions (Conclusion 1, performing a medical, medication, and family history, and Conclusion 4, being aware of medication interactions that are associated with QTc prolongation) are simply prudent medical practice in all settings and provide little useful guidance. In Conclusion 2, the panel takes great pains (even providing us with the breakdown of committee member votes) to state that routine ECG screening is not endorsed. However,

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Conclusion 3 suggests SCD risk minimization strategies should be based on QTc measurements, thus leaving the reader in a quandary. Why common sense Conclusions 1 and 4 and unfounded Conclusions 2 and 3 need codification in this report and in a recently adopted Joint Commission standard for opioid treatment program accreditation is a mystery, especially when one considers that no other QTc-prolonging medications (e.g., any number of antipsychotics, tricyclic antidepressants, or antibiotics) have similar risk minimization reports/standards.

Perhaps some of the confusion in the development of using QTc to monitor SCD risk is that in a heterogeneous family of genetic disorders of cardiac ion channels (generically referred to as long QT syndrome), QTc prolongation greater than 500 msec is associated with a greater than 3% 5-year risk for acute cardiac arrhythmia or SCD.[5] In patients with this disorder who have a QTc < 500 msec, the 5-year risk is 0.5%. The utility of QTc risk stratification in patients with this disorder and their family members is established and risk reduction strategies (e.g., implantable cardiac defibrillator) are effective in reducing SCD. However, similar risk stratification in the general population (discussed above) has remained elusive. One might argue, as CSAT likely has, that the methadone maintained population may not be the equivalent to the general population.

Two nearly 40-year-old studies identified increased QT intervals in methadone patients yet little occurrence of a “sudden death syndrome” in methadone attributed deaths.[6,7] In other words, even when methadone was attributed as cause of death, deaths evolved over time consistent with overdose rather than sudden onset within an hour, a defining characteristic of SCD. Even in the absence of ECG data, this evolving death is inconsistent with SCD. A more recent and conservative (toward being inclusive) estimation is that SCD occurs at a rate of 6 per 10,000 patient years in patients on methadone maintenance,[8] which is lower than the 11.3 per 10,000 person-years in the general population.[9] Although age, gender, and comorbidities cannot be compared between these studies, there does not appear to be an increased risk of SCD in methadone maintained patients compared with the general population.

So, what are we to make of the fact that methadone is associated with QTc prolongation? Furthermore, does identifying an at-risk population allow us to reduce mortality? A systematic approach to reviewing the literature on methadone, QTc, and SCD could provide the needed answers to these questions. Unfortunately, the CSAT expert panel did not use accepted systematic methodology to create and rate their recommendations.

Guideline development consensus statements call for rating the quality of evidence and the strength of resultant recommendations so that readers can adequately assess risks and benefits of implementing recommendations.[10,11] Without this rating, it is difficult to determine the extent to which this report successfully meets its goal of enhancing patient safety. It also prevents the readership from making an informed decision regarding adoption of the report's recommendations. A few examples of how failure to rate evidence may lead to inappropriate weighting or interpretation of the literature are described below.

The reference to basic science research as supporting the report recommendations is problematic. Translating a patch clamp study of an isolated ion channel expressed on a human embryonic kidney cell to clinical outcomes may be difficult because the complex interplay of additional channels, scaffold proteins, and messenger systems cannot be evaluated. There are also issues of scaling in that it is unclear whether concentrations used in cellular studies need to be adjusted up or down to be representative of human physiology. For example, the IC50 in Katchman et al.[12] was 9.8 microM, which is approximately equivalent to a methadone plasma level of 3,300 ng/mL, well beyond the general therapeutic

range of 300 to 900 ng/mL. In addition, because methadone is approximately 90% protein bound, it would take a plasma concentration of 33,000 ng/mL to achieve an in vivo IC50 comparable with that in the cellular model. Until appropriate scaling between in vitro and in vivo studies is understood, it remains premature to base clinical advice on such a study.

Clinical case series such as the FDA Medwatch report by Pearson et al.[13] are another example where closer reading calls into question the veracity of citing this as justification for a risk mitigation strategy to assess QT prolongation in methadone patients. In this uncontrolled series of 59 cases of QT prolongation in methadone patients, there were five reported deaths, of which only one (taking 29 mg of methadone) experienced TdP. The other four deaths were notable for receiving methadone 1,680 mg intravenously, receiving methadone 360 mg intravenously, receiving cisapride, and receiving azithromicin and droperidol in the setting of an acute myocardial infarction. The non-fatal cases of QT prolongation generally were receiving additional QT prolonging medications, had electrolyte abnormalities, or a combination of the two. Thus, the role of methadone in contributing to QT prolongation, and certainly to the associated deaths, is unclear.

Toxicological studies were also used to help create this report. Postmortem determination of cause of death, even in the absence of cardiac disease, cannot validly be used to infer methadone-induced arrhythmia as cause of death. In fact, the National Institutes of Health–National Heart, Lung, and Blood Institute specifically cautions against the use of forensic series when evaluating risk factors for sudden cardiac death.[14]

Multiple cross-sectional studies provide a stronger level of evidence linking methadone with QTc prolongation. Furthermore, these studies have consistently identified approximately 2% of methadone patients as having a QTc >500 msec. There remain inherent difficulties with cross-sectional studies, making it difficult to discern methadone's role as being cause of or simply associated with QTc prolongation. For example, in our own cross-sectional study, 30% of those with a QTc > 500 msec on methadone also had a QTc > 500 msec off of methadone.[15] Anchersen et al.[16] recently identified a genetic mutation for LQTS in two of seven methadone patients with a QTc > 500 msec. Therefore, in several instances where clinically significant QTc prolongation exists, methadone may simply be an innocent bystander and risk mitigation strategies would be needed whether or not the patient was taking methadone. Would part of this risk mitigation include reducing the methadone dose or changing from methadone to an alternative pharmacotherapy, such as R-methadone or buprenorphine?

Methadone dose has been associated less consistently with QTc prolongation. When the dose relationship has been found, it is weak explaining less than 30% of the variability in QTc length.[17,18] In two studies, multiple regression analysis determined that, after controlling for other variables, the average increase in QTc was 0.17 msec per milligram of methadone.[15,18] Other studies have found no direct relationship between methadone dose and QTc.[19,20] Although methadone is associated with prolonged QTc, it is unclear whether a dose threshold can be used as part of SCD risk stratification.

Finally, in two prospective studies of patients initiating methadone for opiate dependence, the average increase in QTc was 34 msec over 16 weeks in one and 10 msec over 12 months in the other.[21,22] The quality of a prospective study makes the relationship between methadone and QTc prolongation more compelling. However, in another controlled study, patients already taking methadone were switched to R-methadone only.[23] This enantiomer provides the opiate agonism inherent in methadone's therapeutic effect but has 3.5-fold lower affinity for the cardiac ion channel implicated in drug-induced SCD than the non-opioid S-methadone.[24] Substituting racemic methadone with R-methadone for 2 weeks

caused a nonsignificant decrease in QTc. Two weeks after switching back to racemic methadone, the QTc was at its base value. Multivariate analysis identified the regression coefficients for serum potassium and calcium as being more than 200 and 600 times larger, respectively, than that of methadone dose. These prospective studies place methadone and QTc in perspective by showing that although changes in QTc may reach statistical significance, there is little clinical significance and other variables such as electrolytes exert a much larger influence on QTc than does methadone.

The question still remains: can adoption of the report's recommendations enhance patient safety? The answer is yes, mostly. The comprehensive history and physical examination is a cornerstone of medicine. The elements of a history and physical examination include medical and family history, medication use, and a cardiac examination. These elements were not created by the expert panel, but if they are not already being performed in methadone clinics, then the report is a helpful reminder. The disservice of this report is in stressing the role of QTc risk evaluation and mitigation as a means to enhance patient safety. As previously stated, there is no evidence that identification of QTc prolongation saves lives in a general population. In fact, the use of QTc monitoring in risk stratification for SCD is rejected by the American Heart Association, the American College of Cardiology Foundation, the Heart Rhythm Society, and the National Heart, Lung, and Blood Institute.[14,25] So, why is CSAT so out of step with the cardiology community? QTc prolongation is absent in the majority of SCD and is not a necessary antecedent to ventricular arrhythmia. In other words, it lacks predictive value and the undue focus on QTc prolongation in the report may divert attention away from other important risk factors and, thereby, decrease patient safety. Until further research establishes modifiable risk factors for SCD in methadone patients, it is premature to adopt all elements of the CSAT report.

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