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Corrected QT Interval Prolongation in Hospitalized Pediatric Patients Receiving Methadone

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Objectives: Methadone is often used in pediatric patients to prevent or treat opioid withdrawal after prolonged sedation. Prolonged corrected QT interval is an important adverse effect of methadone because it can progress to torsades de pointes, a potentially fatal dysrhythmia. The prevalence of corrected QT interval prolongation and contributing risk factors are not well defined in hospitalized pediatric patients receiving methadone. The study purpose was to identify the frequency and risk factors of corrected QT interval prolongation in hospitalized pediatric patients receiving methadone.

Design: Retrospective cohort study.

Setting: Tertiary academic pediatric hospital, University of California Davis Children's Hospital, Sacramento, CA.

Patients: Cohort of 89 pediatric patients (birth to 18 yr) who received at least one dose of methadone while hospitalized.

Interventions: Retrospective data over 7.5 years were obtained from the electronic health record.

Measurements and Main Results: From the cohort, 45 patients (50.6%) had documented corrected QT interval prolongation (≥ 450 ms) during the study period. No episodes of torsades de pointes were identified. In univariate analyses, higher maximum methadone doses were associated with a prolonged corrected QT interval (0.98 vs 0.59 mg/kg/d; odds ratio, 2.56; 1.15–5.70). Corrected QT interval prolongation occurred more frequently in patients with cardiac disease (63% vs 41%; $p = 0.10$). No factors were statistically significant in the multivariate analysis.

Conclusions: In hospitalized pediatric patients receiving methadone, corrected QT interval prolongation was common, but no episodes of torsades de pointes were documented. Risk factors that have been identified in adults were not associated with prolongation in our study population. (*Pediatr Crit Care Med* 2018; 19:e403–e408)

Key Words: adverse effect; corrected QT interval prolongation; methadone; risk factor; torsades de pointes

Methadone, a synthetic opioid agonist, is commonly used in hospitalized pediatric patients for management of opioid withdrawal due to its long half-life and demonstrated efficacy (1). In addition to typical opioid-related adverse effects, methadone can prolong the corrected QT interval (QTc), which can lead to torsades de pointes (TdP), a potentially fatal polymorphic ventricular dysrhythmia (2). According to the American Pain Society, the risk for TdP is increased in adult patients with QTc greater than 450 ms, but most episodes occur when the QTc exceeds 500 ms. Due to a lack of evidence suggesting different thresholds in pediatric patients, these guidelines recommend using values similar to those in adults when assessing cardiac risk in children (2).

The frequency of methadone-induced QTc prolongation is not well known. Studies of adult patients receiving methadone for chronic pain or heroin abuse have reported frequencies of 9–49% when QTc is greater than 450 ms and 2–16% when QTc exceeds 500 ms (3–7). In the first study specifically evaluating the cardiac safety of methadone in pediatric patients, Anghelescu et al (8) found that in pediatric patients being treated for cancer-related pain ($n = 37$), methadone was not associated with clinically significant QTc prolongation, even in the presence of other adult risk factors.

Although the frequency of QTc prolongation is variable, TdP is a rare but serious outcome. Between 1996 and 2002, 43 cases of methadone-related TdP were reported to the U.S. Food and Drug Administration MedWatch, which likely

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underestimates the true prevalence (9). Of the 38 cases that reported age, only one patient was less than 18 years old. Similar to many adult cases reported, this pediatric patient was also receiving two other medications known to prolong the QTc, specifically cisapride and erythromycin (9). This accentuates the role of additional risk factors for QTc prolongation when assessing cardiac risk during methadone therapy.

Risk factors for QTc prolongation and TdP have been clearly identified in adults receiving methadone. These risk factors include female sex, electrolyte abnormalities (i.e., hypokalemia, hypomagnesemia), hepatic dysfunction, structural heart disease, congenital or familial long QT syndrome, and drug-drug interactions that independently prolong the QTc or augment methadone concentrations (2, 3). Similar risk factors have not been defined in pediatric patients. The correlation between dose and risk for QTc prolongation is not well established in either patient population. Some evidence in adult patients suggests greater risk with increasing methadone doses, particularly when the daily dose exceeds 30, 60, or 100 mg in adults (3, 7, 10–13).

Despite the frequent use of methadone for opioid withdrawal in hospitalized pediatric patients, there is no clear characterization of the frequency of QTc prolongation in this population. To address this literature gap, this study was conducted to determine the prevalence of QTc prolongation in pediatric patients receiving methadone at our institution. We also aimed to describe the association between risk factors that have been identified in adults and the risk for QTc prolongation in pediatric patients.

MATERIALS AND METHODS

Study Design

This Institutional Review Board exempt, retrospective, observational cohort study was performed at a tertiary care academic children's hospital in Sacramento, CA. Pediatric patients (birth through 18 yr) who received at least one dose of methadone between April 2008 and October 2015 were identified through a report generated from the electronic health record (EHR). A baseline QTc was not required for inclusion in the study, but the institution did require a QTc prior to initiation of methadone. Patients were excluded if they had a QTc of 450 ms or greater within 30 days prior to the first dose of methadone, had no QTc interval recorded during methadone therapy, received concomitant antiarrhythmic therapy, or had malignancy. Data were collected for all patients who did not meet exclusion criteria.

Data Collected

QTc measurements at baseline and during therapy were obtained from a 12-lead electrocardiogram (ECG), if available, or a documented bedside monitoring strip. The primary endpoint, QTc prolongation, was defined as at least one QTc of 450 ms or greater documented during methadone therapy. If more than one prolonged QTc occurred, the longest QTc documented during therapy was used as the index episode for data collection. Cases of TdP were identified by the primary investigator's review of the EHR problem list. If cardiac arrest or ventricular arrhythmias were documented, these cases were further investigated for occurrence during methadone therapy and clinical suspicion of TdP.

Demographic information was recorded at the time of the longest QTc in patients with prolongation or at time of methadone initiation for patients without prolongation. Data included sex, age in months, weight in kilograms, and length in centimeters. Presence of cardiac disease was defined as any hemodynamically significant heart disease as listed in the EHR, including congenital heart abnormalities, pulmonary hypertension, atrial fibrillation, pericarditis, and heart failure.

For patients with QTc prolongation, the most recent laboratory values obtained within 1 week prior to the longest QTc were recorded for the following: potassium, magnesium, serum creatinine (SCr), and alanine transferase (ALT). For patients who did not have QTc prolongation, the following values during methadone therapy were recorded: lowest potassium, lowest magnesium, highest SCr, and highest ALT. Abnormal laboratory values were defined according to the institution's age-adjusted normal values. Renal dysfunction was defined as glomerular filtration rate (GFR) less than 30 mL/min, as estimated by the Revised Schwartz Estimate (GFR = [0.41 × length in cm/SCr]) (14).

Duration of methadone therapy was recorded as the number of days from the first dose to the last dose of methadone. If a patient received more than one course of methadone, only the first was included in data collection and analysis. The methadone dose associated with the longest QTc was defined as the mean dose (mg/kg/d) during the 3 days prior to the patient's longest QTc. The maximum dose was defined as the largest dose (mg/kg/d) during therapy.

There are a myriad of potential drug-drug interactions with methadone (15). To facilitate data collection, analysis, and interpretation, the authors chose to evaluate the most clinically relevant agents based on the following: the significance of the interaction, formulary and prescribing practices at the institution, and pharmacotherapy for commonly encountered comorbidities in the patient population. For the purpose of this study, the following agents were considered interacting medications: amantadine, amitriptyline, azithromycin, clarithromycin, erythromycin, fluconazole, haloperidol, olanzapine, ondansetron, promethazine, and risperidone. Concomitant medication was defined as at least one documented administration of an interacting medication prior to the longest QTc during methadone therapy or at any time during methadone therapy if no QTc prolongation occurred.

Statistical Methods

Statistical analyses were performed using SAS software Version 9.4 (SAS Institute, Cary, NC) and Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA). A multivariable logistic regression was fit using all covariates of interest in which p value of less than 0.05 was considered significant. Patients with missing values for any of the variables in the multivariable

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model were dropped from the analysis. Results of continuous variables are reported in means ± SD or as median (minimum–maximum) or (interquartile range).

RESULTS

Patients

During the study period, 238 pediatric patients received at least one dose of methadone. Of these, 149 patients were excluded, primarily due to lack of ECG data or due to documented prolonged QTc prior to methadone (**Fig. 1**). Demographic data of the included study cohort ($n = 89$) are displayed in **Table 1**. The majority of patients were male, and approximately one third had cardiac disease. Most of the cohort was less than 1 year old, and patients who experienced QTc prolongation were younger than those who did not (mean, 37.5 vs 53.2 mo; $p = 0.19$). Seventy-five patients had complete data for purposes of the multivariable analysis.

QTc Prolongation and TdP

The primary endpoint of QTc of 450 ms or greater occurred in 45 patients (50.6%), including 18 patients who had a QTc of 500 ms or greater (20.2%) (Fig. 1). The mean longest QTc for the entire study cohort was 453 ± 58 ms (range, 310–620 ms). In patients with prolongation, the mean longest QTc was 496 ± 43 ms compared with 410 ± 34 ms in patients without prolongation. No episodes of TdP were documented during methadone therapy. During a study total of 3,656 days of methadone therapy, one patient had cardiac arrest with asystole and pulseless electrical activity. This episode occurred during a bedside exploratory laparotomy for worsening *Clostridium difficile* colitis, and the last dose of methadone was administered the morning of the event. Four other patients had documented cardiac events or dysrhythmias prior to initiating methadone.

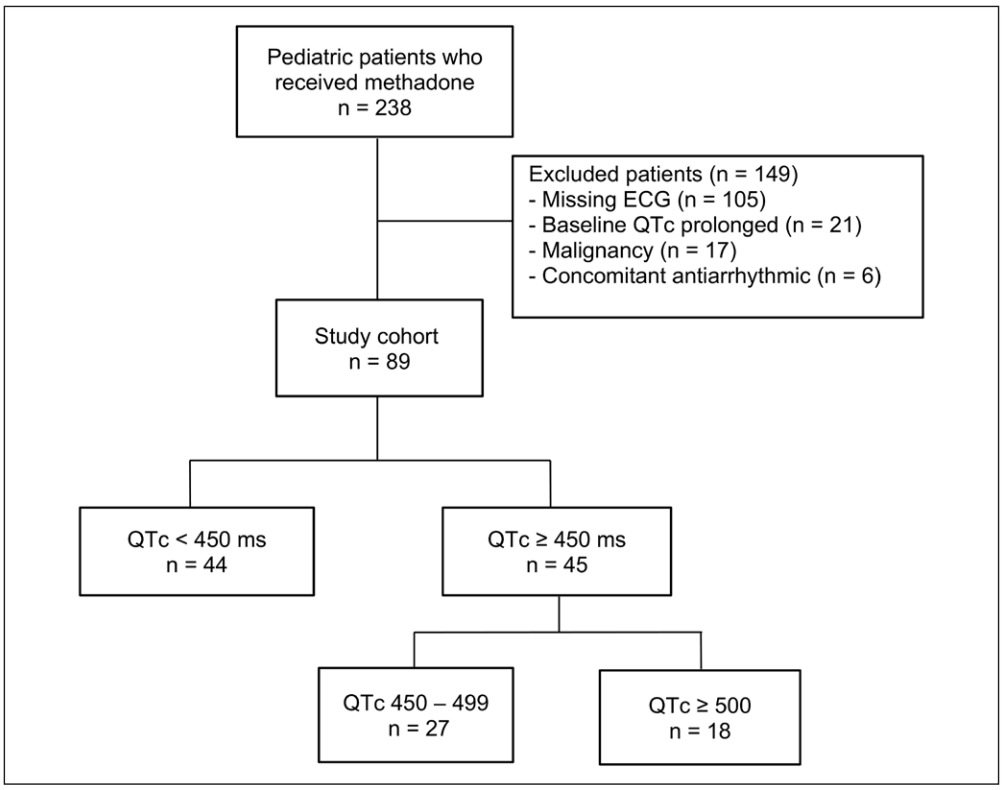

Figure 1. Cohort distribution. ECG = electrocardiogram, QTc = corrected QT interval.

Risk Factors (Univariate Analyses)

QTc prolongation occurred more frequently in patients with cardiac disease compared with patients without cardiac disease (61.1% vs 43.4%; $p = 0.1$) and in patients with elevated ALT (66.7% vs 37.5%; $p = 0.55$). QTc prolongation occurred less frequently in patients with renal dysfunction (40% vs 56%; $p = 0.52$), low magnesium (25% vs 57.8%; $p = 0.31$), and low potassium (41.2% vs 56.4%; $p = 0.16$). QTc prolongation was similar among males and females (51.9% vs 48.7%; $p = 0.76$).

Concomitant Medications

Seventeen patients (20%), four patients (5%), and two patients (3%) received one, two, or three interacting medications, respectively. The most common concomitant medications were ondansetron ($n = 14$), risperidone ($n = 6$), and fluconazole ($n = 5$). Patients who received any interacting medication during methadone therapy experienced less QTc prolongation, although this difference was not significant (44% vs 53.1%; $p = 0.44$).

Methadone Therapy

Duration of methadone therapy was highly variable (range, 1–373 d). Patients who experienced QTc prolongation received more days of methadone (Table 1), and the odds of QTc prolongation increased with increasing days on methadone (odds ratio [OR], 1.03; 95% CI, 1.01–1.05; univariate analysis). In patients who had QTc prolongation, the longest QTc was recorded on median day 24 of therapy (range, 2–173 d). Patients with QTc prolongation received a higher maximum dose (Table 1), and the odds of QTc prolongation increased with increasing maximum dose (OR, 2.56; 95% CI, 1.15–5.7; univariate analysis). Nearly half ($n = 22$; 48.9%) experienced their longest QTc on a dose that was not the largest dose administered to date (i.e., as the methadone dose was decreasing). Thirteen patients (31.1%) experienced their longest QTc on the initial dose.

Multivariable Analysis

The multivariable analysis did not yield any significant results

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TABLE 1. Baseline Demographics and Characteristics of the Study Population

Characteristics	*n* = 89	No Prolonged Corrected QT Interval, *n* = 44	Prolonged Corrected QT Interval, *n* = 45
Age (mo), median (IQR)	13 (5–59)	22 (6.5–63.4)	7.5 (4–38)
< 1, *n* (%)	6 (6.7)	3 (6.8)	3 (6.7)
1–11, *n* (%)	36 (40.4)	13 (29.5)	23 (51.1)
12–35, *n* (%)	18 (20.2)	12 (26.7)	6 (13.3)
36–59, *n* (%)	7 (7.9)	3 (6.8)	4 (8.9)
60–119, *n* (%)	7 (7.9)	5 (11.4)	2 (4.4)
120 or greater, *n* (%)	15 (16.9)	8 (18.2)	7 (15.6)
Female, *n* (%)	37 (41.6)	19 (43.2)	18 (40.0)
Weight (kg), median (IQR)	9.3 (4.9–16.4)	11 (6.6–19.9)	7 (4.7–15.0)
Cardiac disease, *n* (%)	36 (40.5)	14 (31.8)	22 (48.9)
Baseline corrected QT interval (ms), mean ± SD	392 ± 51	387 ± 54	398 ± 48
Days of methadone, median (IQR)	24 (13–46)	17 (9.8–25)	29 (18–67)
Maximum dose (mg/kg/d), median (IQR)	0.59 (0.39–0.97)	0.44 (0.32–0.75)	0.69 (0.40–1.13)

IQR = interquartile range.

(**Table 2**). Most variables produced wide CIs, likely due to the small sample size.

DISCUSSION

To our knowledge, this is the first study to evaluate the cardiac effects of methadone when primarily used for opioid withdrawal in pediatric patients. In our population, half of hospitalized pediatric patients treated with methadone experienced a QTc interval exceeding 450 ms. This is similar to rates seen in adults treated with methadone for chronic pain (12). Marked prolongation (QTc 500 ms or greater) occurred in one of five patients in our study, which is comparable with adults receiving methadone maintenance therapy (7).

In 2016, Anghelescu et al (8) evaluated the cardiac safety of methadone for chronic pain in pediatric patients with malignancy. The study did not report the frequency of QTc prolongation, but the mean QTc during methadone therapy was similar to that seen in our study (446.5 ± 26.3 vs 453 ± 58 ms), suggesting rates of QTc prolongation may have been similar. Our sample size was larger (89 vs 37) and included patients with cardiac disease, which was not addressed in the previous study.

Majority of the patients in this retrospective study were less than 1 year old (Table 1). At our institution, methadone is used almost exclusively for prevention and management of iatrogenic withdrawal following prolonged intubation. Surgical correction of congenital cardiac defects and severe respiratory illness requiring mechanical ventilatory support are two common scenarios that result in prolonged intubation. Methadone is not used to treat neonatal abstinence syndrome at our institution. Although age has not been described as a risk factor for QTc prolongation, our patients were younger than those in the study by Anghelescu et al (8) (mean, 4 vs 16 yr), and patients who experienced QTc prolongation in our study were younger than those who did not. This suggests that there may be an association between younger age and risk of QTc prolongation; future studies should evaluate this possibility.

TABLE 2. Risk Factors in Multivariable Logistic Regression Analysis of 75 Patients Receiving Methadone

Risk Factors	OR (95% CI)
Male	2.20 (0.67–7.21)
Heart disease	2.28 (0.58–9.03)
Renal dysfunction	1.16 (0.18–7.70)
Elevated alanine transferase	0.96 (0.92–1.01)
Hypokalemia	0.33 (0.10–1.13)
Hypomagnesemia	0.25 (0.003–18.12)
Interacting medication	0.47 (0.11–2.13)
Duration of therapy (/d)	1.02 (1.00–1.05)
Maximum dose (mg/kg/d)	1.88 (0.64–5.57)

OR = odds ratio.

At our institution, methadone is primarily used to facilitate opioid weaning rather than to treat pain. When using methadone to prevent withdrawal, there are currently no guidelines for optimal dosing or duration of therapy. A recent systematic review of methadone to prevent or treat iatrogenic withdrawal in pediatric critical care patients found that initial methadone doses and intervals varied widely (0.5–2.3 mg/kg/d, every 6, 8, or 12 hr), and most studies tapered by 10–20% daily (16).

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Practices at our institution reflect this heterogeneity, as differences in clinician preference and patient-specific needs result in a variety of tapering strategies. In general, patients in our study received larger doses of methadone at the beginning of therapy and were slowly weaned off over an average of 41 days. This differed from the stable therapy used to treat cancer-related pain in the study by Anghelescu et al (8).

In our study, a higher maximum dose was associated with an increased frequency of QTc prolongation in the univariate analysis, but not in the multivariable model. When considered on a mg/kg basis, the mean dose for patients who had QTc prolongation in our study (0.98 ± 0.9 mg/kg/d) is likely comparable with the dose found to be associated with prolongation in adults receiving methadone maintenance therapy (100 mg/d) (7). Patients who did not experience QTc prolongation in our study received a maximum daily dose more consistent with the study by Anghelescu et al (8) (0.59 ± 0.42 vs 0.47 ± 0.45 mg/kg/d). It is important to note that in our study, nearly half of patients experienced their longest QTc as the methadone dose was decreasing, and patients with QTc prolongation had a longer duration of methadone therapy. This suggests that cumulative methadone exposure, rather than a specific dose at any given time, could be associated with QTc prolongation. Methadone's unique pharmacokinetic profile, including known accumulation, could contribute to this risk of adverse cardiac effects (2, 17). Further studies should investigate the effects of maximum versus cumulative methadone dose on QTc prolongation.

Although there were no cases of TdP recorded during our study period, we acknowledge that this study was not powered to detect this rare adverse event. It is unlikely that a study could achieve the sample size needed to evaluate TdP, which has been reported as less than 1% of all adverse events related to methadone (9). Despite its rarity, TdP remains clinically relevant as it can lead to a fatal dysrhythmia. Practitioners should remain vigilant, and literature gaps should be addressed to improve our understanding of this adverse event in children.

Our results do not provide evidence that risk factors for QTc prolongation in adults apply to children treated with methadone. This is similar to the findings by Anghelescu et al (8). Although patients with cardiac disease and high ALT (suggesting hepatic dysfunction) did experience more QTc prolongation, these findings were not statistically significant. Other potential risk factors evaluated in the multivariable analysis, such as electrolyte abnormalities, were nonsignificant with wide CIs, likely due to the small sample size. Larger studies are needed to better define risk factors in pediatric patients.

Many clinicians are aware of the multitude of potential drug-drug interactions with methadone. Use of interacting medications was not associated with QTc prolongation in our study. Compared with the cancer patients in the study by Anghelescu et al (8), fewer patients in our study received interacting medications (28% vs 75.7%). This difference in practice could be due to the clinical status of patients after prolonged sedation compared with those who are being treated for chronic cancer-related pain. Provider preferences could also have played a role in use of interacting medications. Our patients were primarily managed by pediatric intensivists and hospitalists, who may be more cautious and/or less familiar with methadone than the clinical pain specialists in the study by Anghelescu et al (8). Both studies found no significant correlation between up to three interacting medications and QTc prolongation. Although this lack of a statistical difference does not prove a lack of clinical effect, it provides evidence to support the cautious use of additional QTc-prolonging agents when there are no alternatives. This would apply to crucial therapies (e.g., antifungal agents) in which the benefit of treatment outweighs risk of QTc prolongation and should include appropriate monitoring (i.e., baseline and steady state QTc measurements). This would not apply to patients requiring antiarrhythmic therapy, as they were excluded from our study population.

Several strengths of our study include the diverse pediatric patient population, which encompassed patients with and without heart disease, as well as patients from birth to 18 years, who were receiving methadone primarily for management of opioid withdrawal. Multivariable analyses were used to assess potential confounding risk factors. The methadone dose was evaluated multiple ways (i.e., maximum daily dose, dose just prior to longest QTc, and relative dose) in order to better understand the correlation between methadone dose and cardiac risk.

The results of our study cannot be widely applied to pediatric patients who are older, have malignancy, or are receiving methadone for chronic pain and/or in an outpatient setting. The results also do not describe pediatric patients with long QT syndrome or concomitant antiarrhythmic therapy. The retrospective design made it difficult to fully control for variability in clinician-driven methadone utilization and the method and timing for QTc monitoring. Prospective studies that include clear, strict protocols or guidelines for dose adjustments, monitoring, and data collection will be more reliable in determining risk factors for QTc prolongation in pediatric patients.

CONCLUSIONS

In the largest evaluation to date of the cardiac effects of methadone in hospitalized pediatric patients, half of the patients experienced a QTc of 450 ms or greater, and one in five had a QTc exceeding 500 ms. We did not find an association between QTc prolongation and risk factors that have been described in adults receiving methadone. Future studies should be a prospective evaluations that include protocols for dosing and monitoring; they should evaluate potentially unique risk factors in children, such as age and cumulative dose of methadone.

REFERENCES

1. Anand KJ, Willson DF, Berger J, et al; *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network: Tolerance and withdrawal from prolonged opioid use in critically ill children. *Pediatrics* 2010; 125:e1208–e1225
2. Chou R, Cruciani RA, Fiellin DA, et al; American Pain Society; Heart Rhythm Society: Methadone safety: A clinical practice guideline from the American Pain Society and College on Problems of Drug

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Dependence, in collaboration with the Heart Rhythm Society. *J Pain* 2014; 15:321–337

3. Stringer J, Welsh C, Tommasello A: Methadone-associated Q-T interval prolongation and torsades de pointes. *Am J Health Syst Pharm* 2009; 66:825–833
4. van den Beuken-van Everdingen MH, Geurts JW, Patijn J: Prolonged QT interval by methadone: Relevance for daily practice? A prospective study in patients with cancer and noncancer pain. *J Opioid Manag* 2013; 9:263–267
5. Fonseca F, Marti-Almor J, Pastor A, et al: Prevalence of long QTc interval in methadone maintenance patients. *Drug Alcohol Depend* 2009; 99:327–332
6. Roy AK, McCarthy C, Kiernan G, et al: Increased incidence of QT interval prolongation in a population receiving lower doses of methadone maintenance therapy. *Addiction* 2012; 107:1132–1139
7. Ehret GB, Voide C, Gex-Fabry M, et al: Drug-induced long QT syndrome in injection drug users receiving methadone: High frequency in hospitalized patients and risk factors. *Arch Intern Med* 2006; 166:1280–1287
8. Anghelescu DL, Patel RM, Mahoney DP, et al: Methadone prolongs cardiac conduction in young patients with cancer-related pain. *J Opioid Manag* 2016; 12:131–138
9. Pearson EC, Woosley RL: QT prolongation and torsades de pointes among methadone users: Reports to the FDA spontaneous reporting system. *Pharmacoepidemiol Drug Saf* 2005; 14:747–753
10. Krantz MJ, Kutinsky IB, Robertson AD, et al: Dose-related effects of methadone on QT prolongation in a series of patients with torsade de pointes. *Pharmacotherapy* 2003; 23:802–805
11. Justo D, Gal-Oz A, Paran Y, et al: Methadone-associated Torsades de Pointes (polymorphic ventricular tachycardia) in opioid-dependent patients. *Addiction* 2006; 101:1333–1338
12. Price LC, Wobeter B, Delate T, et al: Methadone for pain and the risk of adverse cardiac outcomes. *J Pain Symptom Manage* 2014; 48:333–42.e1
13. Martell BA, Arnsten JH, Ray B, et al: The impact of methadone induction on cardiac conduction in opiate users. *Ann Intern Med* 2003; 139:154–155
14. Schwartz GJ, Work DF: Measurement and estimation of GFR in children and adolescents. *Clin J Am Soc Nephrol* 2009; 4:1832–1843
15. Heise W, Romero K, Woosley RL: Risk Categories for Drugs That Prolong QT & Induce Torsades de Pointes (TdP). 2018. Available at: https://www.crediblemeds.org. Accessed August 12, 2015
16. Dervan LA, Yaghmai B, Watson RS, et al: The use of methadone to facilitate opioid weaning in pediatric critical care patients: A systematic review of the literature and meta-analysis. *Paediatr Anaesth* 2017; 27:228–239
17. Leslie ST, Miller RB, Boroda C: Methadone: Evidence of accumulation. *Br Med J* 1977; 1:375

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