Brief Report

Corrected QT Interval Prolongation in Pediatric and Young Adult Patients on Methadone for Cancer-Related Pain

Kevin Madden, MD, Eunji Jo, MS, Janet L. Williams, MBA, MPH, Diane Liu, MS, and Eduardo Bruera, MD
Department of Palliative, Rehabilitation and Integrative Medicine (K.M., J.L.W., E.B.), University of Texas, M.D. Anderson Cancer Center, Houston, Texas; and Department of Biostatistics (E.J., D.L.), University of Texas, M.D. Anderson Cancer Center, Houston, Texas, USA

Abstract

Context. Methadone has been reported to prolong the corrected QT (QTc) interval and increase the risk of torsades de pointes.

Objectives. Our study examined the frequency of QTc prolongation among pediatric and young adult patients starting methadone for cancer pain.

Methods. All patients followed a standardized protocol. Electrocardiograms (ECGs) were obtained at baseline (methadone starting day to 14 days prior), 1−2 weeks, and 4−6 weeks later. QTc values were manually calculated using the Bazett formula. QTc prolongation was defined as ≥460 milliseconds (ms) for prepubertal children, ≥470 ms for pubertal males, and ≥480 ms for pubertal females.

Results. Baseline ECGs were completed in 42 patients. Follow-up ECGs were completed in 38 of 42 (91%) and 31 of 42 (74%) patients at 1−2 weeks and 4−6 weeks, respectively. No patients had prolongation of the QTc at baseline, and 1 of 38 (3%) patients had a prolonged QTc at weeks 1−2. This patient had a history of prolonged QTc that the family did not initially report. No patients had prolongation of the QTc at weeks 4−6. No patients had torsades de pointes or ventricular fibrillation, and none died suddenly.

Median (interquartile range [IQR]) baseline QTc was 391 (377−400) ms; median (IQR) 1−2 week follow-up QTc was 399 (374−411) ms ($P = .05$), and median (IQR) 4−6 week follow-up QTc was 393 (379−423) ms ($P = .01$).

Conclusion. Clinically significant prolongation of the QTc interval occurred only in one patient who had a history of prolonged QTc. Prolonged QTc is rare in this population. J Pain Symptom Manage 2019;58:678−684.

Key Words
Palliative Care, pediatric, pain management, pediatric oncology, cardiotoxicity

Introduction

Pain is the most commonly reported symptom in children with cancer.[1,2] There are many nonpharmacological interventions, but the use of opioids is commonplace. There are many choices of immediate-release and long-acting opioids including methadone. Methadone is a synthetic opioid and an agonist at the μ-, δ-, and κ-opioid receptors. Uniquely, methadone also possesses antagonism at the N-methyl-D-aspartate receptor and is a reuptake inhibitor of both serotonin and norepinephrine[3] that collectively modulate pain in the central nervous system. It has a long half-life,[4,5] high oral bioavailability,[6] and no active metabolites[7] and is the only long-acting opioid available as a liquid. These properties, in addition to its low cost,[8] make methadone an excellent choice for management of pain in children who cannot reliably swallow tablets until approximately 6 to 7 years of age. Its use, however, is likely limited because of a combination of perceived family resistance[9] and its complex pharmacokinetics and pharmacodynamics.[10]

Address correspondence to: Kevin Madden, MD, Department of Palliative, Rehabilitation and Integrative Medicine, University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1414, Houston, TX 77030, USA. E-mail: kmadden@mdanderson.org

Accepted for publication: May 31, 2019.

0885-3924/$ - see front matter
https://doi.org/10.1016/j.jpainsymman.2019.05.021

Potential side effects of methadone are the same as those with other opioids and include constipation, nausea, and sedation. At high doses, myoclonus, hallucinations, and respiratory insufficiency may occur.[11,12] Many drug-drug interactions that alter the metabolism and elimination of methadone[13,14] and can increase the risk of prolongation of the corrected QT (QTc) interval and subsequent development of torsades de pointes (TdP), a life-threatening cardiac arrhythmia, are possible.[15–17] The myriad of medications commonly used in pediatric oncology, including diphenhydramine, ondansetron, granisetron, famotidine, pantoprazole, macrolide antibiotics, and azole antifungals,[18] also independently prolong the QTc, furthering the risk of TdP. Concerns about prolongation of the QTc interval[15,19–22] are tempered with small, retrospective studies in children[23–26] which suggest methadone is safe to use in children with cancer.

The purpose of this retrospective study was to evaluate the frequency of and factors associated with prolongation of the QTc interval in children and young adults receiving methadone. This cohort of patients followed a standardized protocol of obtaining electrocardiograms (ECGs) at specific intervals, and so, our study possesses more internal controls that previous studies lack.

Methods

Subjects

The Institutional Review Board at The University of Texas M.D. Anderson Cancer Center approved this study. We conducted a retrospective electronic medical record review of patients with cancer referred to the pediatric supportive care service for management of pain between January 1, 2016, and November 1, 2018. The electronic medical record was reviewed for demographic variables, medical history, medication regimen, and laboratory data.

Administration of Methadone

Two board-certified pediatric and palliative care physicians assessed all children and young adults who received methadone. Family history was obtained for a person with a history of prolonged QTc interval, family history of prolonged QTc interval, or a family history of sudden, unexplained death. Methadone was initiated as a long-acting opioid in children and young adults who had 1) nociceptive, 2) neuropathic, or 3) nociceptive with neuropathic pain that was not controlled with oral immediate-acting opioids (defined as needing more than four as needed doses per 24 hours). Patients were started on methadone in both the outpatient and inpatient setting for pain. The choice of immediate-acting opioid for breakthrough pain was left to the discretion of the physician.

Children and young adults were started on methadone at standard analgesic starting doses of 0.1 mg/kg/dose every 12 hours by mouth,[27,28] with a maximum of 5 mg by mouth every 12 hours, or an equianalgesic dose of methadone[29] if they were not opioid-naive. For children unable to swallow tablets, methadone elixir was used. For those children and young adults who could take tablets, it was left to the prescribing physicians' discretion to round the dose up or down to the nearest 2.5 mg interval. All outpatient children and young adults were monitored by phone for three consecutive days after starting methadone to assess the efficacy and side effects; inpatient children and young adults were evaluated daily to ensure the effectiveness of dose and absence of side effects.

Electrocardiographic Assessments

ECGs were performed uniformly for all patients in the study. A baseline ECG was performed on the day of starting of methadone if not completed within the preceding 14 days. Follow-up ECGs were performed 1–2 weeks and 4–6 weeks after methadone initiation. Documentation of why follow-up ECGs were not performed was completed for all patients.

ECGs were performed using the ELI 350 electrocardiography machine (Mortara Instruments Inc., Milwaukee, WI). QTc values for analysis were manually computed by a board-certified pediatric critical care medicine physician with years of experience working in a pediatric cardiac intensive care unit. The standard formula described by Bazett[30] was used to calculate the QTc. The QT and preceding RR interval were measured in lead II with one beat from a standard 12-lead ECG tracing at 25 mm/second paper speed at 10 mm/mV amplitude using ECG calipers.

A prolonged QTc interval is variable depending on age and sex; the 99 to 99.5 percentile values in prepubescent males and females is ≥460 ms; for pubertal males, it is ≥470 ms, and for pubertal females, it is ≥480 ms.[31] Puberty was defined using the standard sexual maturity rating scale (Tanner stages).[32]

Contributing Factors to Increasing QTc Interval

Other medications can increase the QTc interval and were classified by the risk of causing TdP based on the Arizona Center for Education and Research on Therapeutics.[18] This website identifies three risk categories: 1) drugs that carry a risk of TdP, 2) drugs that increase the QTc interval and/or, in some reports, that have been associated with TdP but lack substantial evidence for causing TdP at this time, and 3) drugs that carry a risk of TdP and/or increase the QTc interval under certain conditions, such as patients with congenital long QT syndrome, who had drug overdose, or who coadministered interacting drugs.

Table 1
Baseline Characteristics of Patients

Characteristic	$n = 42$ (%)
Median age (range)	16 (1–25)
Female	18 (43%)
Race	
White	27 (64%)
Hispanic	8 (19%)
Asian	2 (5%)
African American	2 (5%)
Others/unknown	3 (7%)
Primary oncologic diagnosis	
Sarcoma	20 (48%)
Leukemia/lymphoma	15 (36%)
Central nervous system tumor	3 (7%)
Neuroblastoma	2 (5%)
Laryngeal cancer	1 (2%)
Ovarian cancer	1 (2%)

Medications were further classified by whether they prolong the QTc interval by directly increasing the QTc interval or indirectly increasing the QTc interval by inhibition of methadone metabolism that can increase the serum concentration of methadone, thus elevating the risk of increasing the QTc interval.

Abnormalities in potassium, calcium, and magnesium levels have been identified as risk factors for increasing the QTc interval.[33] We documented these laboratory values if they were collected on the day the ECG was performed.

Statistical Analysis

Summary statistics are used to describe patients' characteristics such as age, gender, race, primary oncologic diagnosis, and the frequency of prolonged QTc. Wilcoxon signed-rank test was used to compare the change of the QTc from baseline to each follow-up ECG time point. Repeated-measures analysis was used to assess the change of the QTc over time, total methadone daily dose (TMDD), serum electrolytes, and concomitant medications that may affect the QTc.

All computations were carried out in SAS 9.4 (SAS Institute Inc., Cary, NC) and R 3.4.2.

Results

The baseline characteristics of patients are presented in Table 1. The median (range) age of patients was 16 years.[1–25] Most patients were male (57%) and white (64%) and had a diagnosis of sarcoma (48%).

Fig. 1 shows patient accrual to the study. Forty-two consecutive patients were included in the study; no patients were excluded because of baseline prolongation of the QTc interval, personal or familial history of prolonged QTc, or a family history of sudden, unexplained death. All 42 patients were evaluated at baseline (100%). Thirty-eight of 42 (91%) patients had an ECG performed at weeks 1–2, and 31 of 42 (74%) patients had an ECG performed at weeks 4–6.

Table 2 shows the longitudinal QTc interval assessments at baseline, 1–2 weeks, and 4–6 weeks. The Wilcoxon signed-rank test was used to compare each patient's baseline QTc value with their subsequent QTc values. Compared with the baseline QTc interval, the QTc interval at 1–2 weeks ($P = .05$) and 4–6 weeks ($P = .01$) were statistically, significantly longer. Only one patient (1/38, 3%), a 20-year-old male, had a prolonged QTc interval. This patient had a prolonged QTc interval of 513 ms while on methadone which occurred at weeks 1–2. The patient's baseline QTc was 451 ms. He had no new medications added between the baseline QTc and week 1–2 QTc, and he also did not have any electrolyte abnormalities at any time point. Before the initiation of methadone, the patient and family reported no past medical history of a prolonged QTc, a family history of a prolonged QTc, or a family history of sudden, unexplained death. After the second ECG demonstrated a prolonged QTc interval, the patient and family were reinterviewed, and at this time, they reported the patient did have a prior history of a prolonged QTc that was not disclosed at the initial history. The patient had no evidence of TdP or ventricular fibrillation on this ECG. Clinically, he had a normal heart rate and blood pressure and had no syncope or presyncopal vertigo. Methadone was immediately discontinued, and a repeat ECG performed 24 hours later showed a QTc interval of 436 ms.

Table 3 shows the risk factors for prolonged QTc. Most patients were on at least one medication that directly prolongs the QTc and one medication that indirectly prolongs the QTc while also taking methadone. The number of medications known to directly ($P = .15$) or indirectly ($P = .88$) prolong QTc was not significantly associated with QTc. A 1 mEq/L decrease in serum potassium was significantly associated with a 17 ms increase in the QTc interval ($P = .02$). There was no association between TMDD and QTc interval ($P = .96$), and the serum levels of calcium ($P = .17$) and magnesium ($P = .53$) were not significantly correlated with QTc. Age greater than 18 years ($P = .11$), gender ($P = .84$), and TMDD ($P = .06$) were not associated with an increased QTc interval.

All patient deaths were related to the progression of their cancer and not due to a cardiac arrhythmia.

Discussion

To our knowledge, this is the first study to examine the association between methadone and QTC interval in consecutive children and young adults on a standardized protocol of obtaining ECGs. Our study found that while there was a significant increase in the QTc interval with the addition of methadone, there was no clinical significance to these increased

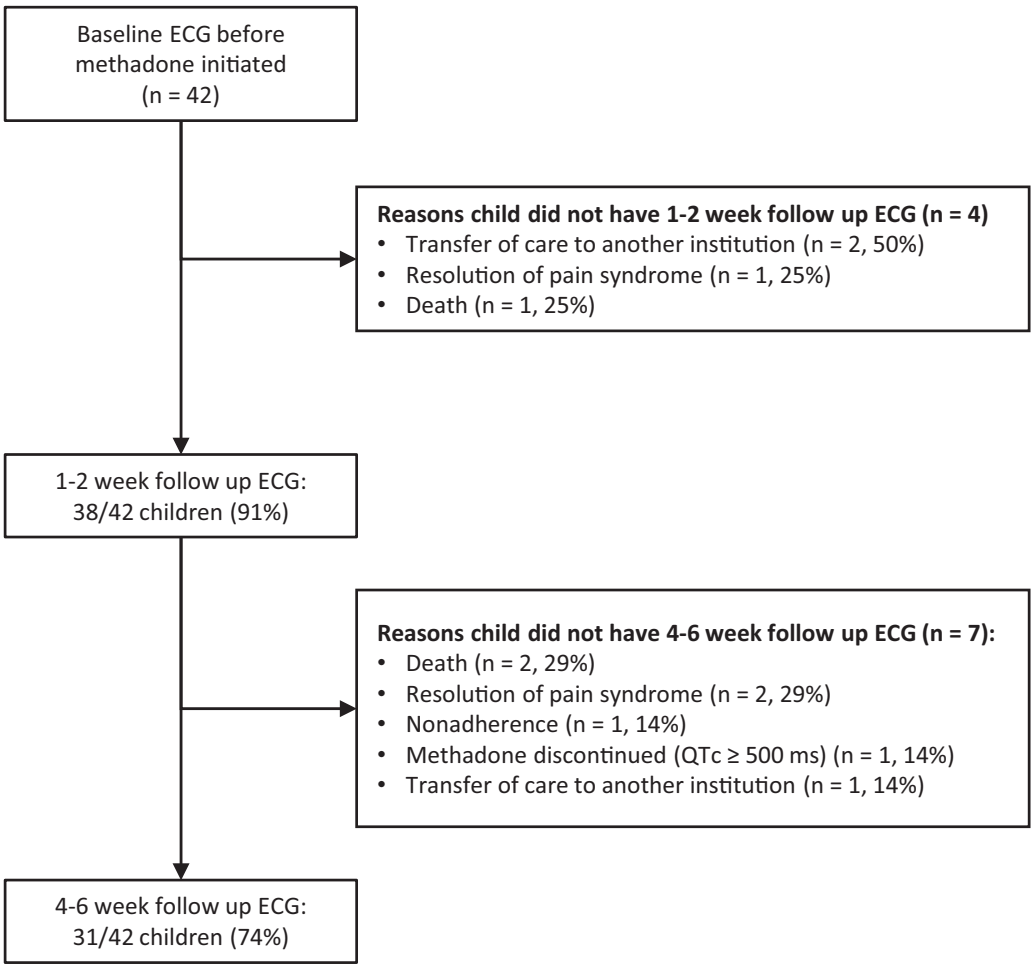

Fig. 1. Patient accural. ECG = electrocardiogram; QTc = corrected QT.

values. The singular exception was the patient who had an undisclosed history of prolonged QTc that was not divulged at the time of starting methadone.

The use of methadone in children can be challenging. While it has been shown to be an effective medication for the treatment of cancer-related pain in children and young adults,[23,34–40] concerns about its use by physicians[10] and families[41] persist. While the apprehensions of families are rooted in the stigmatization of methadone as a medication for addiction, most physician worries are related to its potential to prolong the QTc interval that leads to a fatal cardiac arrhythmia. While methadone has been reported to directly increase the QTc interval, this is an uncommon phenomenon[25] in children. Professional society guidelines for the use of methadone in children do not provide much reassurance or clarity. The American Pain Society (APS) guidelines draw

Table 2
Longitudinal QTc Interval Assessments at Baseline, 1–2 Weeks, and 4–6 Weeks

Variable	Baseline (n = 42)	1–2 Weeks (n = 38)	P Value[a]	4–6 Weeks (n = 31)	P Value[b]
Median QTc, ms (IQR)	391 (377–400)	399 (374–411)	.05	393 (379–423)	.01
QTc ≥ upper limit of normal[c]	0 (0%)	1 (2.6%)	—	0 (0%)	—
Median methadone dose, mg (IQR)	—	7.5 (5–10)	—	5 (4.4–10)	—
Median methadone dose, mg/kg/dose (minimum–maximum)	—	0.1 (0.05–0.21)	—	0.1 (0.05–0.32)	—

IQR = interquartile range; QTc = corrected QT.
[a]Comparison of individual QTc at baseline vs. 1–2 weeks (Wilcoxon signed-rank test).
[b]Comparison of individual QTc at baseline vs. 4–6 weeks (Wilcoxon signed-rank test).
[c]Upper limit of normal for: prepubertal children = 460 ms; pubertal males = 470 ms; pubertal females = 480 ms.

Table 3
Known Risk Factors for QTc Prolongation

Variable	1–2 Weeks $n = 38$	4–6 Weeks $n = 31$	*P* Value
Number (%) of patients on medications that			
Directly increase QTc	33 (8)	25 (81)	
Indirectly increase QTc	23 (61)	16 (52)	
Number [median (IQR)] of medications that			
Directly increase QTc	1 (1–2)	1 (1–2)	
Association with QTc			.15
Indirectly increase QTc	1 (0–1)	0 (0–1)	
Association with QTc			.88
Serum electrolyte levels, median (IQR)			
Calcium (mg/dL)	8.9 (8.6–9.4)	9.6 (8.6–9.8)	
Association with QTc			.17
Magnesium (mg/dL)	1.8 (1.7–1.9)	1.9 (1.8–2.2)	
Association with QTc			.53
Potassium (mEq/L)	4.0 (3.7–4.3)	4.1 (3.9–4.3)	
Association with QTc			.02[a]

IQR = interquartile range; QTc = corrected QT.
[a]One unit decrease of potassium (mEq/L) was significantly correlated with a 17 ms increase in the QTc.

conclusions extrapolated from adult data[28] and therefore are unlikely to apply to our patient population. For example, the APS recommends reconsideration of methadone if the QTc is greater than 450 ms but less than 500 ms.

Additionally, a recent expert consensus white paper on the use of methadone in hospice and palliative care[42] does not provide any guidance for its use in children. This lack of data has ostensibly led pediatric palliative care physicians to "default" to the threshold values of a prolonged QTc interval in adults of 450 ms and 500 ms.[41] Furthermore, some pediatric-specific QTc studies use 450 ms as the defined value of a prolonged QTc interval.[22,26] Yet there is evidence that the 99–99.5% normal values for the QTc interval in children are ≥460 ms for prepubertal children, ≥470 ms for pubertal males, and ≥480 ms for pubertal females.[31] Not being aware of these higher QTc thresholds may lead to significant consequences for children as methadone, as well as other medications that prolong the QTc interval, may be discontinued hastily out of concern for causing a cardiac arrhythmia.

Although there was a significant difference between the baseline QTc interval and the QTc interval at 1–2 weeks and 4–6 weeks, it should be reassuring that the only patient who had a prolonged QTc during the study period had a history of prolonged QTc that was not divulged at the time of starting methadone. He never suffered any clinical sequelae, and his QTc normalized quickly after discontinuing methadone. Aside from this patient, the observed increase in QTc interval with the addition of methadone never approached age-defined prolongation of the QTc interval. Knowing that the measured QTc interval is only but a snapshot in time, it is important to note that no patient had any clinical manifestations of a prolonged QTc, namely syncope or sudden death.

Our findings concerning other variables that might affect the QTc interval including serum electrolytes, TMDD, and the number of concomitant medications that also increase the QTc interval are consistent with those of other studies conducted in children and young adults. We found an association between a lower potassium level and an increased QTc interval. Other electrolytes such as calcium and magnesium had no correlation. Similar to other studies,[22,24–26] we also found no association between the QTc and other medications taken simultaneously with methadone that may prolong the QTc interval.

There are many strengths to our study. All patients adhered to a strict standard of care protocol with regard to dosing of methadone and obtaining baseline and follow-up ECGs. Additionally, the data of consecutively seen children and young adults were analyzed, thereby minimizing some of the selection bias that can come with retrospective studies.

There are several limitations to our study. The retrospective nature certainly does not account for all confounding variables that may potentially influence the QTc interval. Additionally, our study was conducted in a single, tertiary care cancer center, and so, our conclusions may not be applicable to children and young adults who use methadone for other pain syndromes. Finally, the limited number of other QTc-prolonging medications, or other medications that interact with methadone to prolong the QTc, makes it difficult to make strong generalizations about the safety of methadone in patients who may be on many medications that can also affect the QTc interval.

Conclusions

The findings of our study should be reassuring to pediatric practitioners that methadone is a safe medication to use in children and young adults with cancer-

related pain. Monitoring potassium levels, especially for an inpatient or a critically ill patient, might be warranted. Obtaining a thorough history from the patient and family regarding a prior history or prolonged QTc interval, a family history of a prolonged QTc interval, or a family history of sudden, unexplained death is crucial. The difference in QTc for each patient from baseline to weeks 1−2 and weeks 4−6 was statistically significant, but not clinically relevant. Baseline ECGs may identify individuals at risk for further prolongation of the QTc interval, but our study indicates that if the baseline ECG is normal and there are no other risk factors, follow-up ECGs may not be warranted.

Disclosure/Conflict of Interests

The authors have no financial disclosures or conflicts of interest.

References

1. Wolfe J, Grier HE, Klar N, et al. Symptoms and suffering at the end of life in children with cancer. N Engl J Med 2000; 342:326−333.

2. Wolfe J, Orellana L, Ullrich C, et al. Symptoms and distress in children with advanced cancer: prospective patient-reported outcomes from the PediQUEST study. J Clin Oncol 2015;33:1928−1935.

3. Davis MP, Walsh D. Methadone for relief of cancer pain: a review of pharmacokinetics, pharmacodynamics, drug interactions and protocols of administration. Support Care Cancer 2001;9:73−83.

4. Sawe J. High-dose morphine and methadone in cancer patients. Clinical pharmacokinetic considerations of oral treatment. Clin Pharmacokinet 1986;11:87−106.

5. Gourlay GK, Cherry DA, Cousins MJ. A comparative study of the efficacy and pharmacokinetics of oral methadone and morphine in the treatment of severe pain in patients with cancer. Pain 1986;25:297−312.

6. Dale O, Sheffels P, Kharasch ED. Bioavailabilities of rectal and oral methadone in healthy subjects. Br J Clin Pharmacol 2004;58:156−162.

7. Chow RM, Issa M. Methadone. In: Yong RJ, Nguyen M, Nelson E, Urman RD, eds. Pain Medicine: An Essential Review. Cham: Springer International Publishing, 2017: 157−158.

8. Benedetti C, Dickerson ED. Criteria for opioid selection. J Pain Symptom Manage 2000;19:410−411.

9. Madden K, Park M, Liu D, Bruera E. Practices, attitudes, and beliefs of palliative care physicians regarding the use of methadone and other long-acting opioids in children with advanced cancer. J Palliat Med 2018;21:1408−1413.

10. Roth M, Davies D, Friebert S, et al. Attitudes and practices of pediatric oncologists regarding methadone use in the treatment of cancer-related pain: results of a North American Survey. J Pediatr Hematol Oncol 2013;35: 103−107.

11. Elsayem A, Bruera E. Methadone-induced respiratory depression in a patient with a history of alcoholism. J Palliat Med 2005;8:1062−1066.

12. Benitez-Rosario MA, Salinas Martin A, Gomez-Ontanon E, Feria M. Methadone-induced respiratory depression after discontinuing carbamazepine administration. J Pain Symptom Manage 2006;32:99−100.

13. Kharasch ED, Regina KJ, Blood J, Friedel C. Methadone pharmacogenetics: CYP2B6 polymorphisms determine plasma concentrations, clearance, and metabolism. Anesthesiology 2015;123:1142−1153.

14. Ferrari A, Coccia CP, Bertolini A, Sternieri E. Methadone–metabolism, pharmacokinetics and interactions. Pharmacol Res 2004;50:551−559.

15. Krantz MJ, Kutinsky IB, Robertson AD, Mehler PS. Dose-related effects of methadone on QT prolongation in a series of patients with torsade de pointes. Pharmacotherapy 2003; 23:802−805.

16. Walker PW, Klein D, Kasza L. High dose methadone and ventricular arrhythmias: a report of three cases. Pain 2003; 103:321−324.

17. 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.

18. Woosley RaR KA. QTdrugs List. Available from www.Crediblemeds.org. Accessed November 20, 2018.

19. Gupta A, Lawrence AT, Krishnan K, Kavinsky CJ, Trohman RG. Current concepts in the mechanisms and management of drug-induced QT prolongation and torsade de pointes. Am Heart J 2007;153:891−899.

20. 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.

21. Lovell AG, Protus BM, Saphire ML, et al. Evaluation of QTc interval prolongation among patients with cancer using enteral methadone. Am J Hosp Palliat Care 2019;36: 177−184.

22. Schwinghammer AJ, Wilson MD, Hall BA. Corrected QT interval prolongation in hospitalized pediatric patients receiving methadone. Pediatr Crit Care Med 2018;19: e403−e408.

23. Rasmussen VF, Lundberg V, Jespersen TW, Hasle H. Extreme doses of intravenous methadone for severe pain in two children with cancer. Pediatr Blood Cancer 2015;62: 1087−1090.

24. 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.

25. Madden K, Park M, Liu D, Bruera E. The frequency of QTc prolongation among pediatric and young adult patients receiving methadone for cancer pain. Pediatr Blood Cancer 2017;64.

26. Heath TS, Greenberg RG, Hupp SR, et al. Effects of methadone on corrected QT interval prolongation in critically ill children. J Pediatr Pharmacol Ther 2018;23: 119−124.

27. Schechter NL, Berde CB, Yaster M. Pain in infants, children, and adolescents, 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 2003:850.

28. Chou R, Cruciani RA, Fiellin DA, et al. Methadone safety: a clinical practice guideline from the American pain society and college on problems of drug dependence, in collaboration with the heart rhythm society. J Pain 2014;15:321–337.

29. Bruera E, Sweeney C. Methadone use in cancer patients with pain: a review. J Palliat Med 2002;5:127–138.

30. Bazett HC. The time relations of the blood-pressure changes after excision of the adrenal glands, with some observations on blood volume changes. J Physiol 1920;53:320–339.

31. Johnson JN, Ackerman MJ. QTc: how long is too long? Br J Sports Med 2009;43:657–662.

32. Kliegman R, Behrman RE, Nelson WE. Nelson textbook of pediatrics, Edition 20/ed. Phialdelphia, PA: Elsevier. 2016:53-54.

33. Diercks DB, Shumaik GM, Harrigan RA, Brady WJ, Chan TC. Electrocardiographic manifestations: electrolyte abnormalities. J Emerg Med 2004;27:153–160.

34. Anghelescu DL, Faughnan LG, Hankins GM, Ward DA, Oakes LL. Methadone use in children and young adults at a cancer center: a retrospective study. J Opioid Manag 2011;7:353–361.

35. Davies D, DeVlaming D, Haines C. Methadone analgesia for children with advanced cancer. Pediatr Blood Cancer 2008;51:393–397.

36. Habashy C, Springer E, Hall EA, Anghelescu DL. Methadone for pain management in children with cancer. Paediatr Drugs 2018;20:409–416.

37. Madden K, Bruera E. Very-low-dose methadone to treat refractory neuropathic pain in children with cancer. J Palliat Med 2017;20:1280–1283.

38. Sabatowski R, Kasper SM, Radbruch L. Patient-controlled analgesia with intravenous L-methadone in a child with cancer pain refractory to high-dose morphine. J Pain Symptom Manage 2002;23:3–5.

39. Shir Y, Shenkman Z, Shavelson V, Davidson EM, Rosen G. Oral methadone for the treatment of severe pain in hospitalized children: a report of five cases. Clin J Pain 1998;14:350–353.

40. Madden K, Mills S, Dibaj S, et al. Methadone as the initial long-acting opioid in children with advanced cancer. J Palliat Med 2018;21:1317–1321.

41. Madden K, Liu D, Bruera E. Attitudes, beliefs, and practices of pediatric palliative care physicians regarding the use of methadone in children with advanced cancer. J Pain Symptom Manage 2019;57:260–265.

42. McPherson ML, Walker KA, Davis MP, et al. Safe and appropriate use of methadone in hospice and palliative care: expert consensus white paper. J Pain Symptom Manage 2019;57:635–645.e4.