Because we don't know when we will die, we get to think of life as an inexhaustible well. Yet everything happens only a certain number of times, and a very small number really. How many more times will you remember a certain afternoon of your childhood, some afternoon that is so deeply a part of your being that you can't even conceive of your life without it? Perhaps four or five times more, perhaps not even that. How many more times will you watch the full moon rise? Perhaps twenty. And yet it all seems limitless.

Paul Bowles, *The Sheltering Sky*

Methadone for Analgesia in Children

Kevin Madden, M.D.

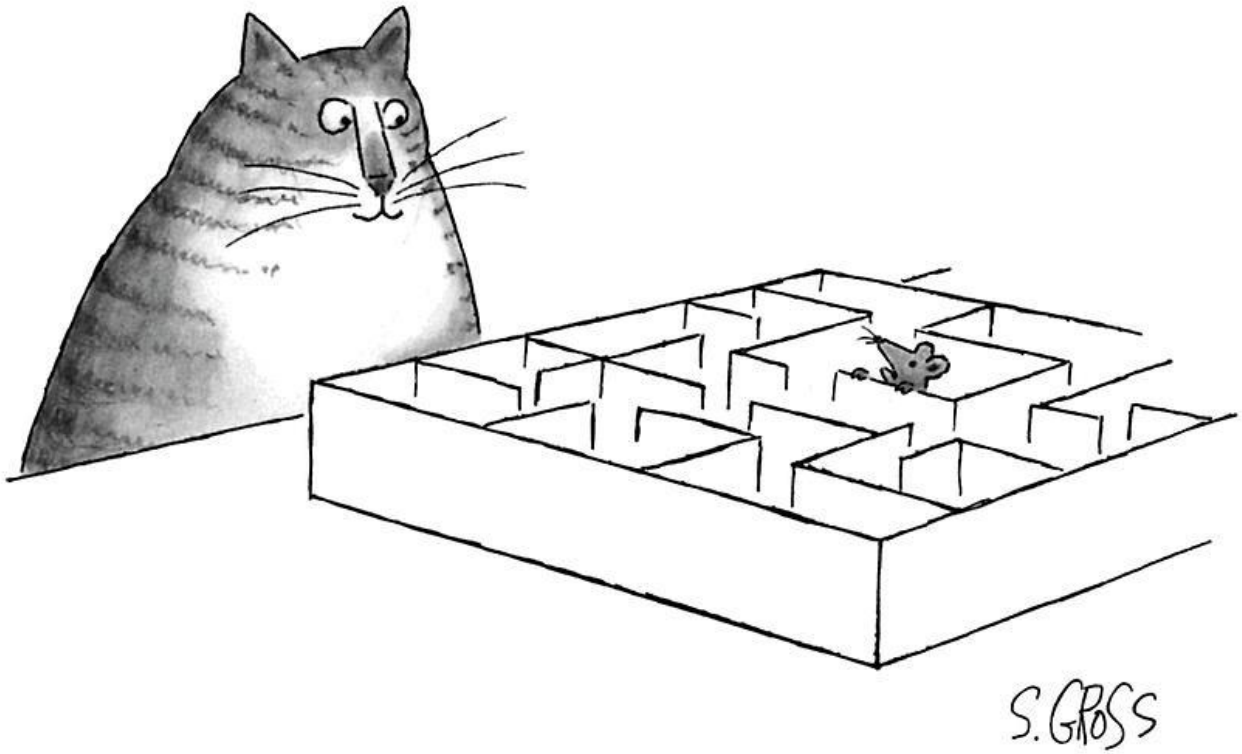
Department of Palliative, Rehabilitation and Integrative Medicine

kmadden@mdanderson.org

@madden_kevin

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Disclosures



"Well, you don't look like an experimental psychologist to me."

Objectives

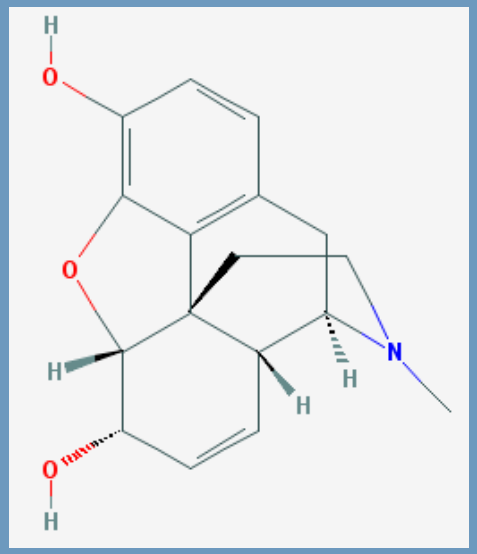
1. How is methadone different?
2. Dosing of methadone
3. Attitudes and beliefs of palliative care providers about methadone
4. Prolongation of the QTc interval while on methadone
5. Methadone as the initial long-acting opioid
6. Methadone and Cannabidiol
7. Methadone for refractory neuropathic pain

What makes Methadone different?

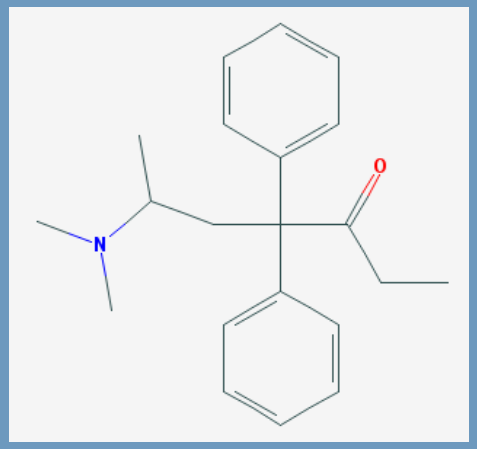
- Chemical structure
- Pharmacokinetics
- Dual mechanism of action
- Drug interactions
- Cardiac conduction abnormalities
- ***COST***

Structure

- Most opioids have a structure that resembles morphine



- Methadone shares structural similarities to propoxyphene



Pharmacokinetics

- Oral bioavailability: 80-90%
  - $t_{½}$ = 3.8 - 62 hours
  - Inter-patient variability
  - Dependent on CYP450 metabolism
  - Delayed toxicity
- No active metabolites
  - Renal excretion is pH dependent
- Highly lipophilic

Pharmacokinetics

- **Tricky pharmacology**
  - $t_{½}$ = 3.8 - 62 hours[8]
  - Time to reach steady state is usually 4 - 5 $t_{½}$
- Therefore methadone steady state reached in:

19 hrs to 12 days

5 Drugs for the Price of 1

- Racemic mixture (d- and l- isomers)
  - Dextrorotatory (*S*-methadone)
    - NMDA receptor antagonism
    - 5-HTP and norepinephrine re-uptake blockade
  - Levorotatory (*R*-methadone)
    - Higher affinity for mu, kappa and delta opioid receptors

Drug Interactions

- Methadone is metabolized by:
  - CYP3A4
  - CYP2C19
  - CYP2D6
  - CYP1A2

Increases Methadone Levels

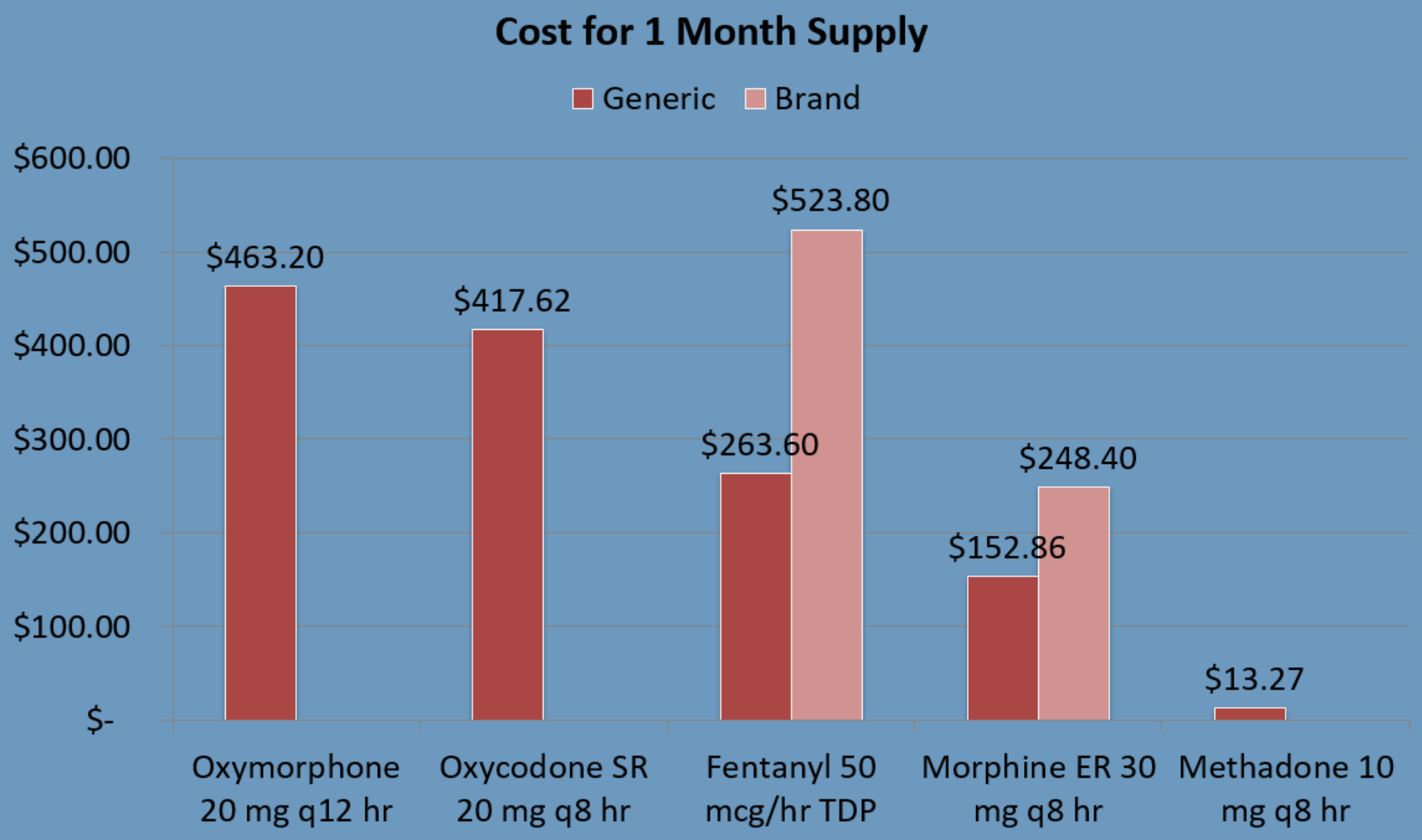
- By inhibiting metabolism
  - CYP3A4
    - **Antifungals: ketoconazole, fluconazole, itraconazole**
    - **Antibiotics: ciprofloxacin, erythromycin, clarithromycin, INH**
    - **Benzodiazepines: clonazepam, diazepam**
    - Grapefruit juice, cimetidine, urinary alkalinzers
    - Calcium-channel blockers: verapamil, diltiazam
  - **SSRIs** (CYP3A4, CYP1A2, CYP2D6)
    - 3A4: nefazadone > fluvoxamine > paroxetine > fluoxetine
    - 1A2: fluvoxamine > paroxetine > sertraline > fluoxetine > nefazadone
- ***Methadone also inhibits the metabolism of TCAs and SNRIs***

Decreases Methadone Levels

- By increasing metabolism
  - CYP3A4
    - Anti-epileptic drugs: phenobarbital, phenytoin, carbamazepine
    - Rifampicin, rifabutin
    - **Dexamethasone**
    - Antiretrovirals: ritonavir, abacavir, amprenavir, efavirenz, nelfinavir and nevirapine

Opioid Costs

Average Wholesale Price (AWP)



How to Approach with Parents

- Get Buy In First -> don’t say the M word
- But END conversation with “The medication is called methadone”
- Add in some historical perspective

A Controversial History

Myth or Fact?

- Developed in Germany during WWII due to morphine shortage
  –> MYTH
- Spasmolytic research at high doses
  –> FACT
- Analgesic properties not expected
  –> FACT
- Not used as an analgesic until after WWII
  –> FACT
- Nomenclature of dolophine (methadone)
  - Adolph
    –> MYTH
  - Dolor (pain) + fin (end)
    –> FACT

History Continued

- 1950's: U.S. Public Health Service hospitals use as treatment for opioid abstinence syndrome
- 1960's: N.Y.C. Health Research Council funded research in opioid craving and withdrawal prevention in heroin addiction
- 1971: Methadone maintenance treatment programs expanded to 25,000 patients
- 1973: Closed system established for prescribing and dispensing of methadone for maintenance
- 1976: APA sued for pharmacies to dispense methadone as an analgesic

Anticipatory Guidance

- Lay out clear expectations (and undersell…)
- Establish realistic goals -> what’s the target?
- Establish boundaries

Dosing of Methadone

Two Different Ends of the Spectrum

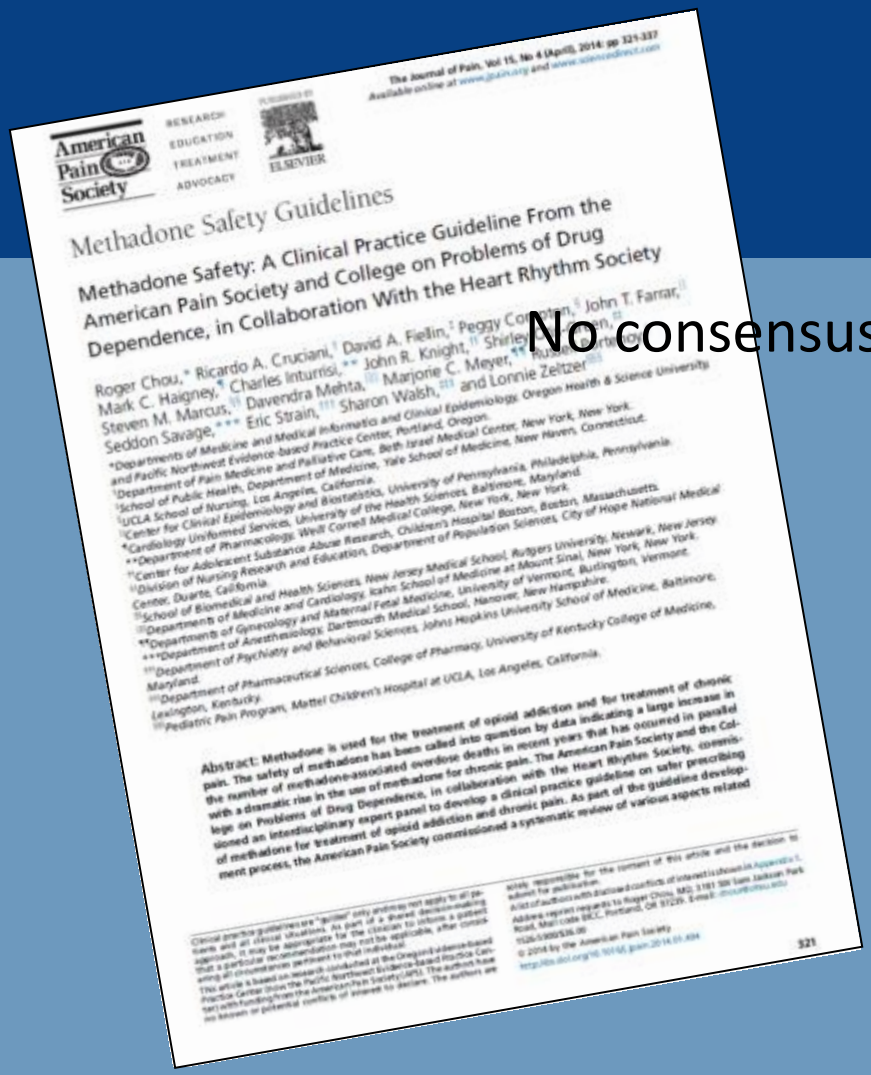
Dose too large

Opioid induced neurotoxicity (OIN)
Excessive somnolence, hallucinations, myoclonus

Dose too small

Poorly controlled pain

No consensus on starting doses



The Journal of Pain, Vol 15, No 4 (April), 2014: pp 321-337
Available online at www.jpain.org and www.sciencedirect.com

American Pain Society — RESEARCH EDUCATION TREATMENT ADVOCACY — ELSEVIER

Methadone Safety Guidelines

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

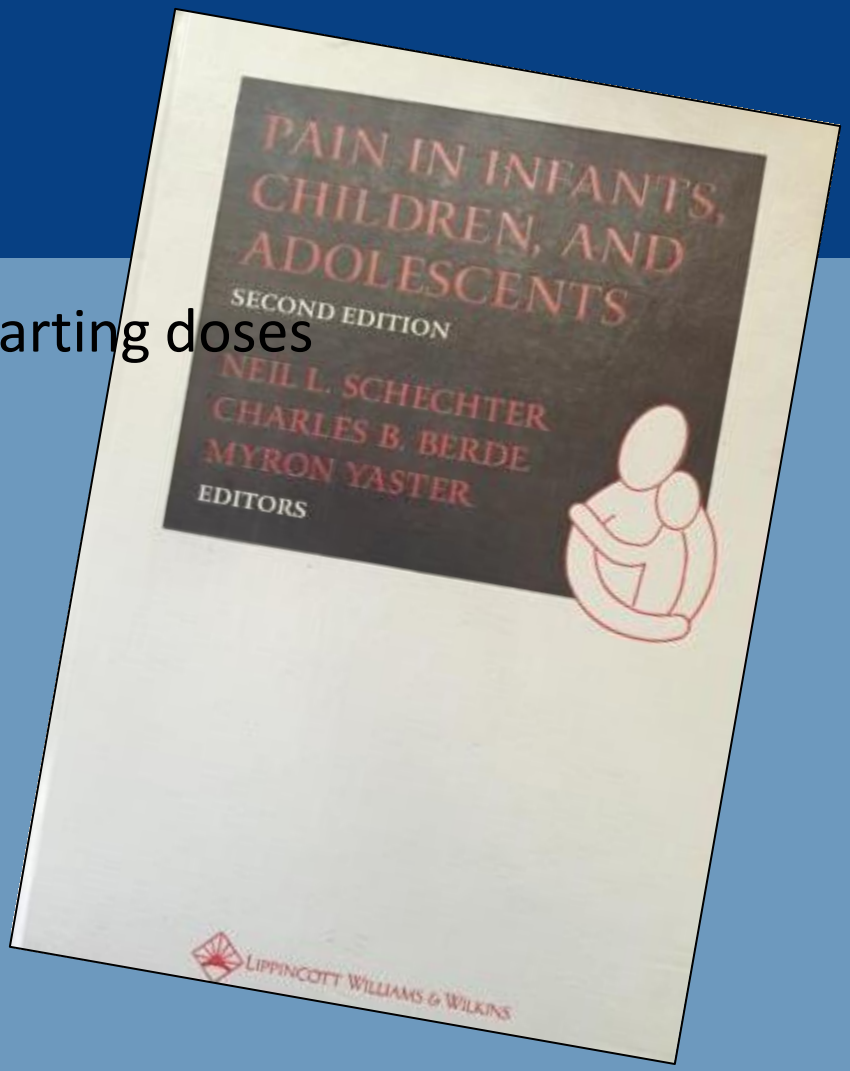
Roger Chou,* Ricardo A. Cruciani,† David A. Fiellin,‡ Peggy Compton,§ John T. Farrar,‖ Mark C. Haigney,¶ Charles Inturrisi,** John R. Knight,†† Shirley [illegible],‡‡ Russell [illegible],§§ Steven M. Marcus,‖‖ Davendra Mehta,¶¶ Marjorie C. Meyer,*** [illegible] Seddon Savage,*** Eric Strain,††† Sharon Walsh,‡‡‡ and Lonnie Zeltzer‡‡‡

*Departments of Medicine and Medical Informatics and Clinical Epidemiology, Oregon Health & Science University and Pacific Northwest Evidence-based Practice Center, Portland, Oregon.
†Department of Pain Medicine and Palliative Care, Beth Israel Medical Center, New York, New York.
‡Department of Medicine, Yale School of Medicine, New Haven, Connecticut.
§School of Public Health, Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania.
‖School of Nursing, Los Angeles, California.
¶UCLA School of Medicine and Biostatistics, University of Pennsylvania, Baltimore, Maryland.
**Center for Clinical Epidemiology and Biostatistics, University of the Health Sciences, Baltimore, Maryland.
††Cardiology Uniformed Services, University of the Health Sciences, New York, New York.
‡‡Department of Pharmacology, Weill Cornell Medical College, New York, New York.
§§Department of Substance Abuse Research, Children's Hospital Boston, Boston, Massachusetts.
‖‖Center for Adolescent Substance Abuse Research, Department of Population Sciences, City of Hope National Medical Center, Duarte, California.
¶¶Division of Nursing Research and Education, Department of Medicine, New Jersey Medical School, Rutgers University, Newark, New Jersey.
***School of Biomedical and Health Sciences, Department of Medicine at Mount Sinai, New York, New York.
†††Departments of Medicine and Cardiology, Icahn School of Medicine, University of Vermont, Burlington, Vermont.
‡‡‡Departments of Gynecology and Maternal Fetal Medicine, University of New Hampshire.
§§§Department of Anesthesiology, Dartmouth Medical School, Hanover, New Hampshire.
‖‖‖Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland.
¶¶¶Department of Pharmaceutical Sciences, College of Pharmacy, University of Kentucky College of Medicine, Lexington, Kentucky.
***Pediatric Pain Program, Mattel Children's Hospital at UCLA, Los Angeles, California.

Abstract: Methadone is used for the treatment of opioid addiction and for treatment of chronic pain. The safety of methadone has been called into question by data indicating a large increase in the number of methadone-associated overdose deaths in recent years that has occurred in parallel with a dramatic rise in the use of methadone for chronic pain. The American Pain Society and the College on Problems of Drug Dependence, in collaboration with the Heart Rhythm Society, convened an interdisciplinary expert panel to develop a clinical practice guideline on safer prescribing of methadone for treatment of opioid addiction and chronic pain. As part of the guideline development process, the American Pain Society commissioned a systematic review of various aspects related

Clinical practice guidelines are "guidelines" only and do not apply to all patients and all clinical situations. As part of a shared decision-making approach, it may be appropriate for the clinician to inform a patient that a particular recommendation pertinent to that individual. [illegible] using all circumstances pertinent to that individual.
This article is based on research conducted at the Oregon Evidence-Based Practice Center (Oregon Health & Science University) and the Pacific Northwest Evidence-Based Practice Center (Pacific Northwest Evidence-Based Practice Center) with funding from the American Pain Society (APS). The authors have no known or potential conflicts of interest to declare. The authors have [illegible] solely responsible for the content of this article and the decision to submit for publication.
A list of authors with disclosed conflicts of interest is shown in Appendix 1.
Address reprint requests to Roger Chou, MD, 3181 SW Sam Jackson Park Road, Mail code BICC, Portland, OR 97239. E-mail: [illegible]
1526-5900/$36.00
© 2014 by the American Pain Society
http://dx.doi.org/10.1016/j.jpain.2014.01.494

321



PAIN IN INFANTS, CHILDREN, AND ADOLESCENTS
SECOND EDITION
NEIL L. SCHECHTER
CHARLES B. BERDE
MYRON YASTER
EDITORS
LIPPINCOTT WILLIAMS & WILKINS

0.1 mg/kg (maximum of 5 mg/dose) every 6 to 8 hours[13]

0.1-0.2 mg/kg every 4 to 8 hours[14]

World Health Organization

"Loading doses" of 0.1-0.2 mg/kg
every 4 hours for 2 to 3 doses
then every 6 to 12 hours[15]

In the absence of data, all opinions are equal.

Practices, Attitudes, and Beliefs of Palliative Care Physicians Regarding the Use of Methadone and Other Long-acting Opioids in Children with Advanced Cancer

Madden K, et. al. (2018). Journal of palliative medicine, 21(10), 1408-1413.

General attitudes and beliefs for different long acting opioids

	Comfort Level	Cost Prevents Prescribing	Family Resistance
	"Comfortable" to "Extremely Comfortable" n (% of respondents)	"Frequently" to "Extremely Frequently" n (% of respondents)	"High" to "Extremely High" n (% of respondents)
Morphine ER	84 (94%)	4 (5%)	21 (24%)
Fentanyl TDP	76 (85%)	18 (21%)	5 (6%)
Hydromorphone ER	33 (37%)	26 (31%)	3 (4%)
Methadone	75 (84%)	3 (3%)	44 (51%)
Oxycodone ER	75 (84%)	25 (29%)	18 (21%)

	Ease of Administration	Ease of Titration	Analgesic Effect	Side Effect Profile
	"Easy" to "Extremely Easy" n (% of respondents)	"Easy" to "Extremely Easy" n (% of respondents)	"Effective" to "Extremely Effective" n (% of respondents)	"Well Tolerated" to "Extremely Well Tolerated" n (% of respondents)
Morphine ER	39 (44%)	47 (55%)	70 (84%)	49 (57%)
Fentanyl TDP	73 (83%)	18 (21%)	57 (69%)	66 (77%)
Hydromorphone ER	24 (29%)	20 (25%)	44 (56%)	29 (36%)
Methadone	68 (77%)	41 (48%)	61 (73%)	71 (83%)
Oxycodone ER	36 (41%)	44 (51%)	63 (76%)	53 (62%)

Madden K, et. al. (2018). Journal of palliative medicine, 21(10), 1408-1413.

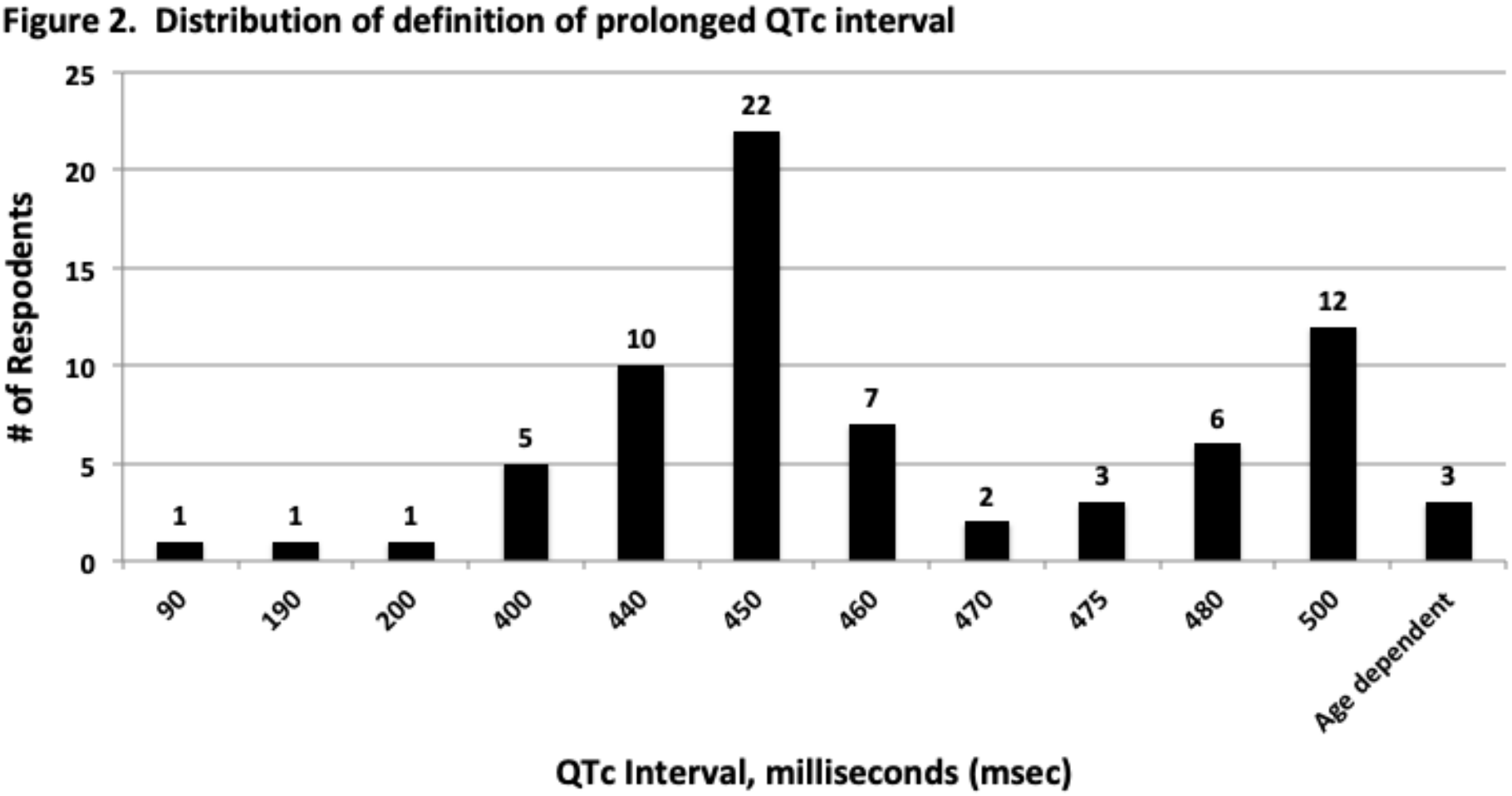
Attitudes, Beliefs, and Practices of Pediatric Palliative Care Physicians Regarding the Use of Methadone in Children With Advanced Cancer

Madden K., et. al. (2019). Journal of Pain and Symptom Management, 57(2), 260-265.

23% of pediatric palliative care physicians **CANNOT** prescribe methadone

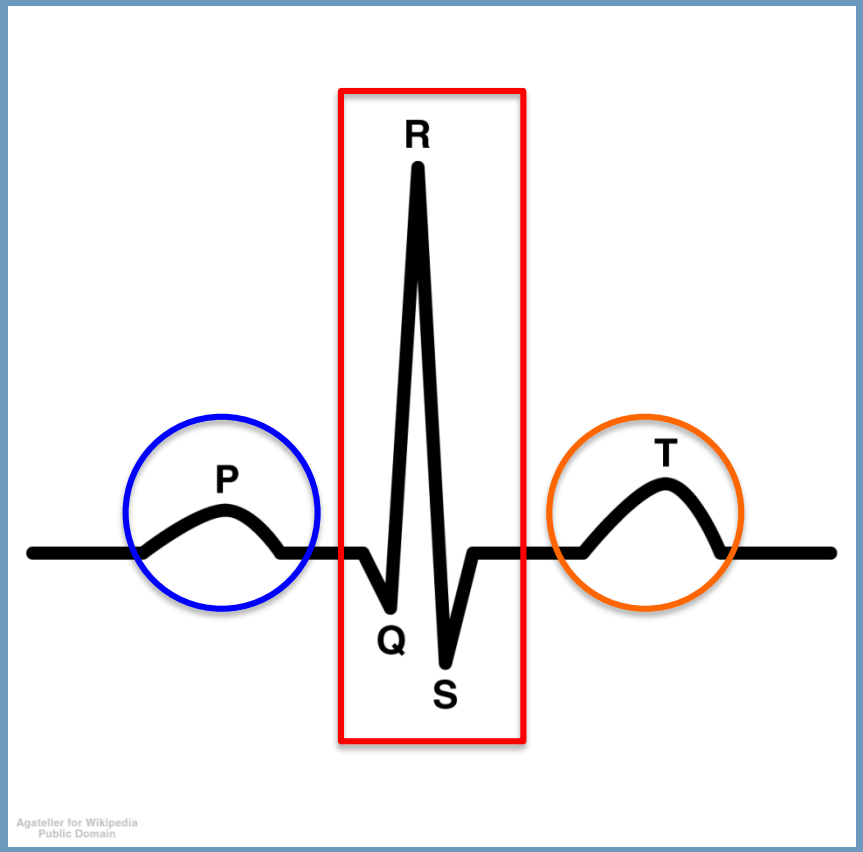
"Institution-specific policies that limit who can prescribe methadone"

Do we agree what is a prolonged QTc?



Madden K., et. al. (2019). Journal of Pain and Symptom Management, 57(2), 260-265.

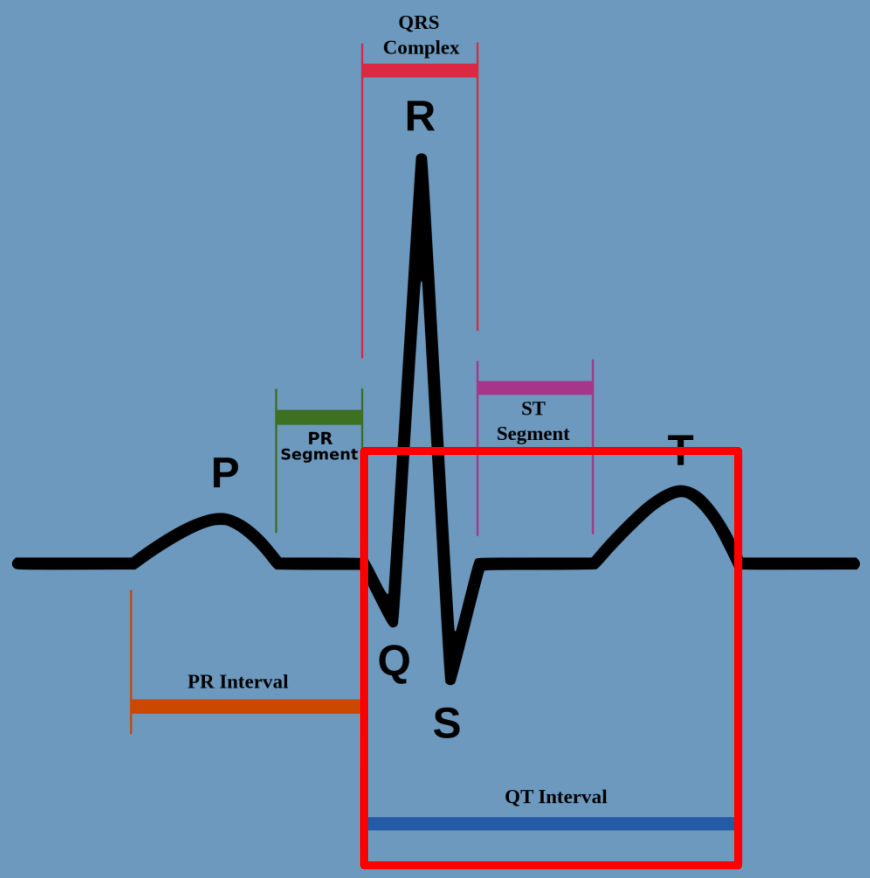
What is the QT Interval?



Normal PQRST

- P wave – atrial depolarization (contraction)
- QRS complex – ventricular depolarization (contraction)
- T wave – repolarization of ventricles (relaxation)

What is the QT Interval?

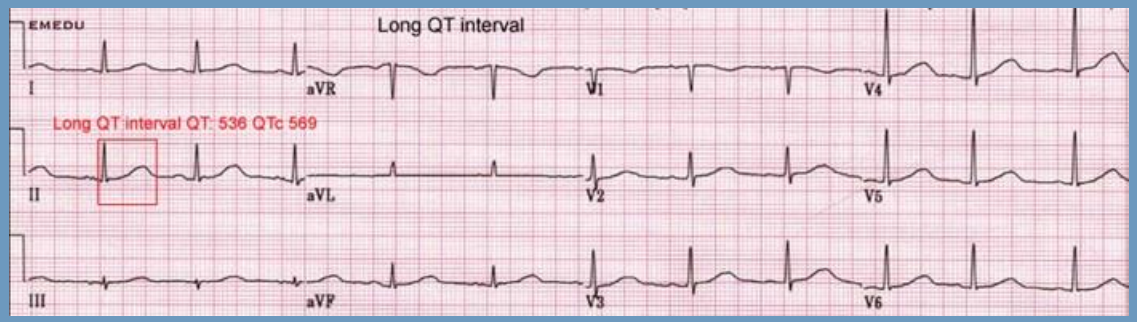


Cardiac Intervals and Segments

- QT Interval – measured from the beginning of the QRS complex to the end of the T wave

Why do we “correct” the QT interval?

- “The QT interval is related to heart rate in an inverse exponential relationship”
- In plain English:
  - As heart rate ***increases*** QT ***decreases***



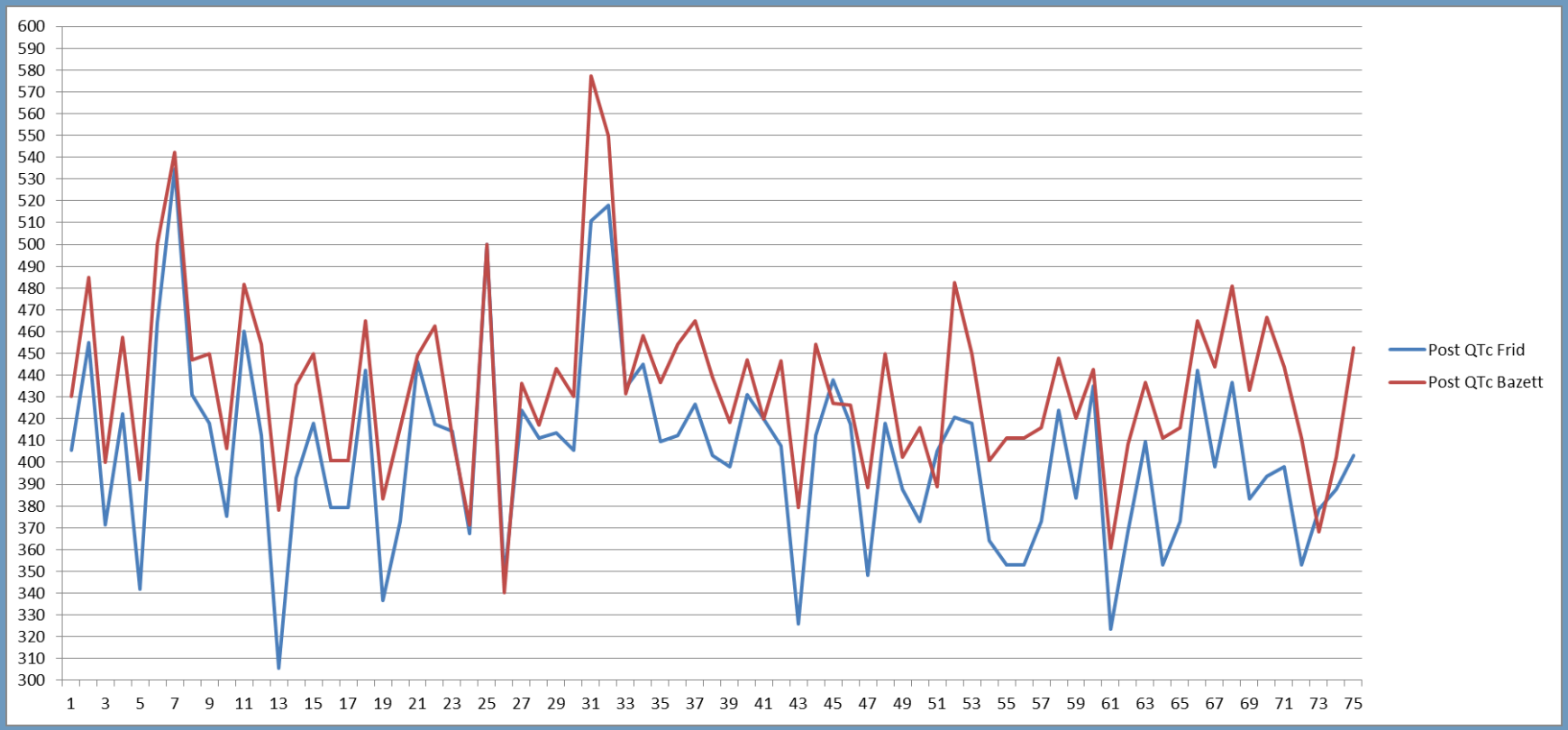
  - Especially important in children whose resting heart rates are much higher than adults

How do we "correct" the QT interval?

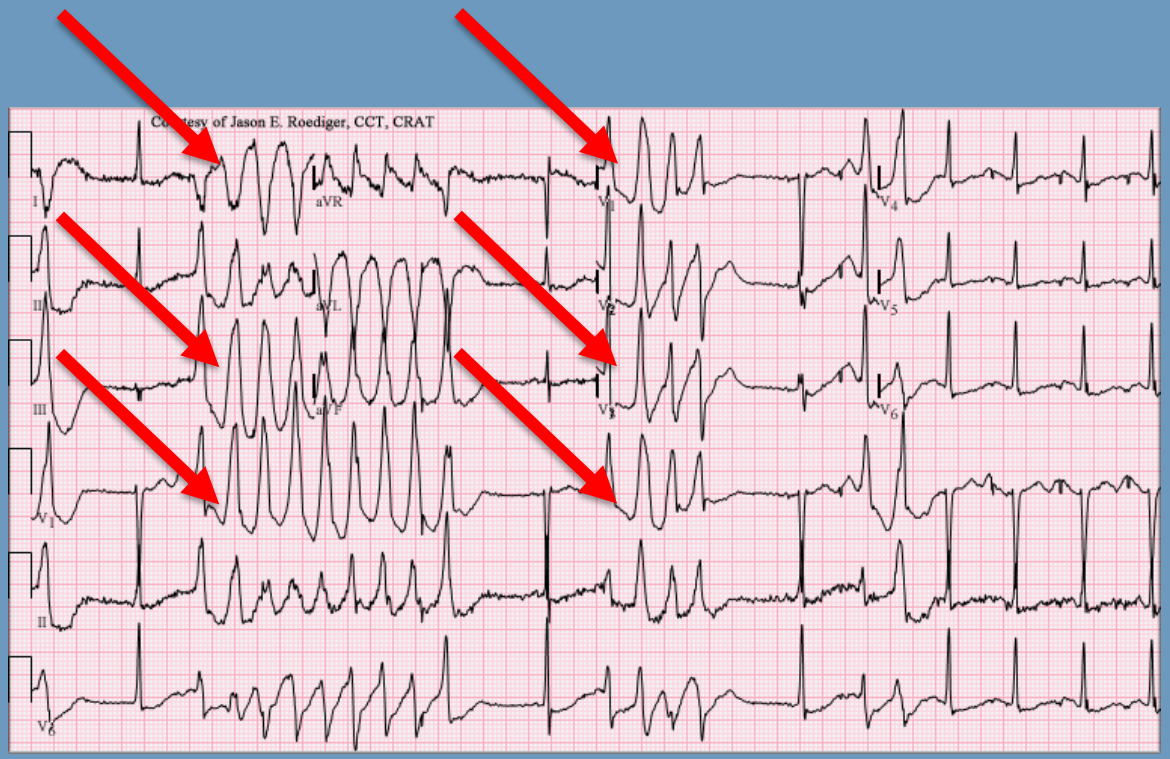
- There are at least ***17 unique*** QT correction formulas which have been published

Formula	Equation	N	Mean Age (Range)
Bazett	$QT / \sqrt{RR}$	39	26 (14-53)
Fridericia	$QT / \sqrt[3]{RR}$	50	26 (2-81)
Baseline Correction	$QT / \sqrt[37]{RR}$	--	--
Framingham	$QT + 0.154 (1 - RR)$	5,018	44 (28-62)
Hodges	$QT + 1.75 (HR - 68)$	607	(20's-80's)

Why Does it Matter?

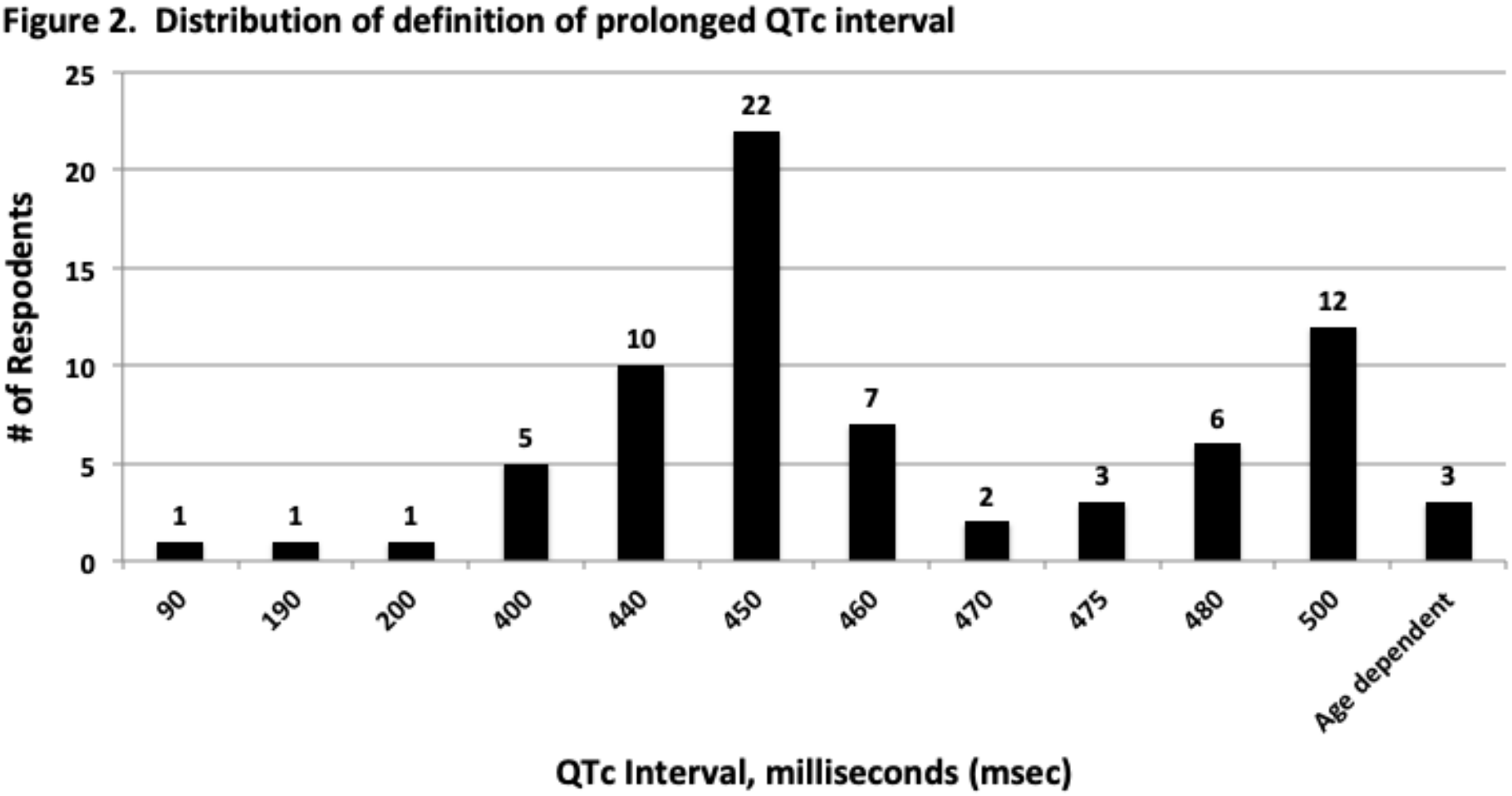


Why is the QTc important?



As QTc increases, so does the risk of Torsade de Pointes – a polymorphic ventricular tachycardia that can lead to sudden cardiac death

Do we agree what is a prolonged QTc?



Madden K., et. al. (2019). Journal of Pain and Symptom Management, 57(2), 260-265.

When is a QTc prolonged?

When is a QTc Prolonged?

460 ms pre-pubertal children

470 ms pubertal males

480 ms pubertal females

99.5% normal values

What Do You Do When QTc is Prolonged?

460 – 500 ms

- Review all medications that may prolong the QTc
- Consider modifying doses/discontinuing medications

≥ 500 ms

- Review all medications that may prolong the QTc
- Discontinue medications that prolong QTc

Implications

- Methadone discontinued prematurely when it may still benefit a patient
- Not easy to transition over to another long acting opioid due to long half-life of methadone

The Frequency of QTc Prolongation Among Pediatric and Young Adult Patients Receiving Methadone for Cancer Pain

Madden K, et. al. (2017). Pediatric Blood & Cancer, 64(11), e26614.

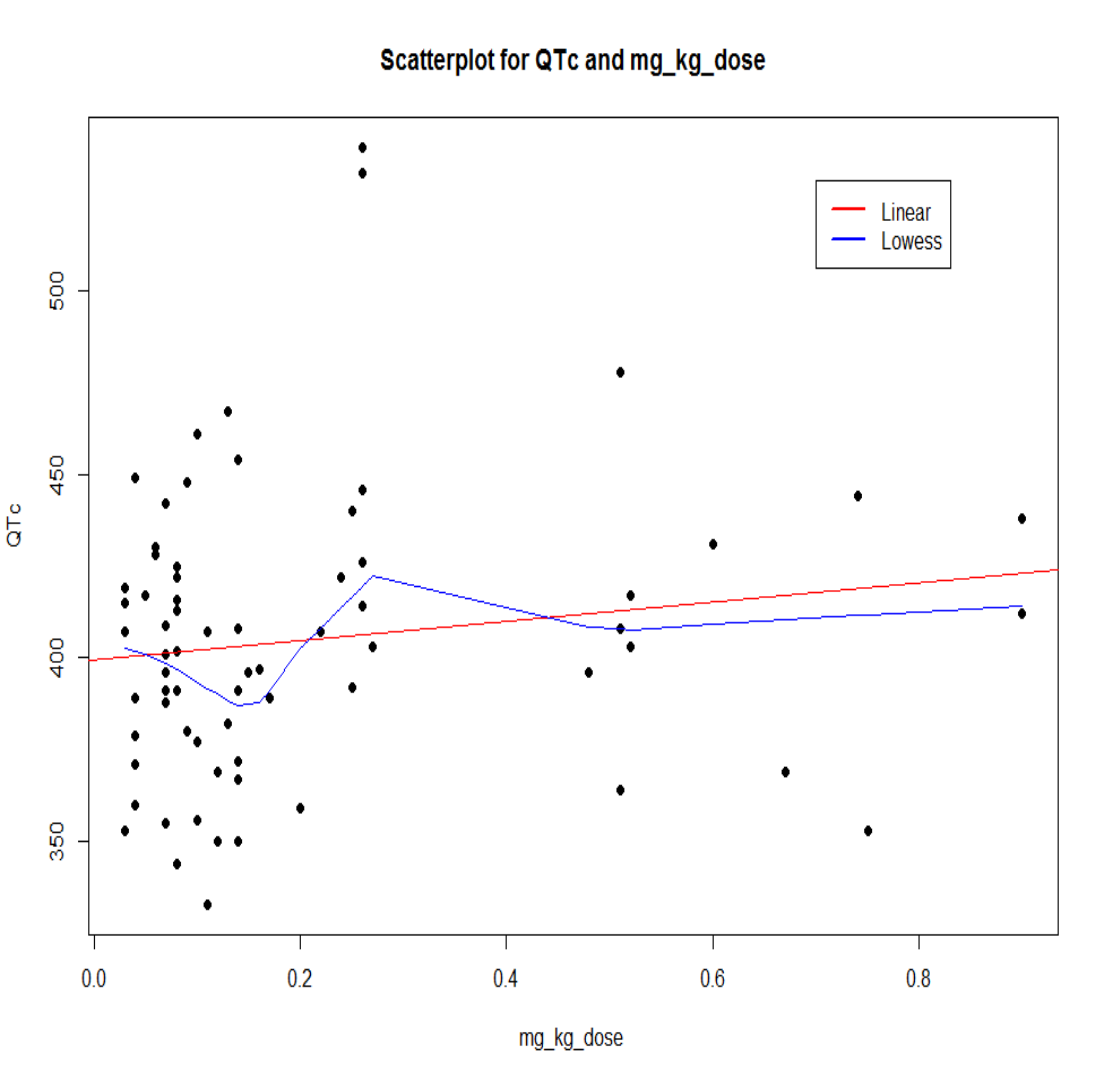
What did we find?

TABLE 2 QTc (Bazett) before and after methadone treatment

	Before Methadone	After Methadone	P-value
Prolonged QTc (> 470 ms), 95% CI	0/14 (0%) (0 – 12.6%)	1/25 (4%) (0.1 – 11.7%)	
Median (IQR) QTc in patients who had ECG before and after (n = 14)	441 (401, 444) ms	428 (411, 447) ms	0.9637
Median (IQR) QTc in patients who only had ECG after (n = 11)		416 (402, 437) ms	
Median (IQR) QTc in all patients (n = 25)		420 (408, 444) ms	

Madden K, et. al. (2017). Pediatric Blood & Cancer, 64(11), e26614.

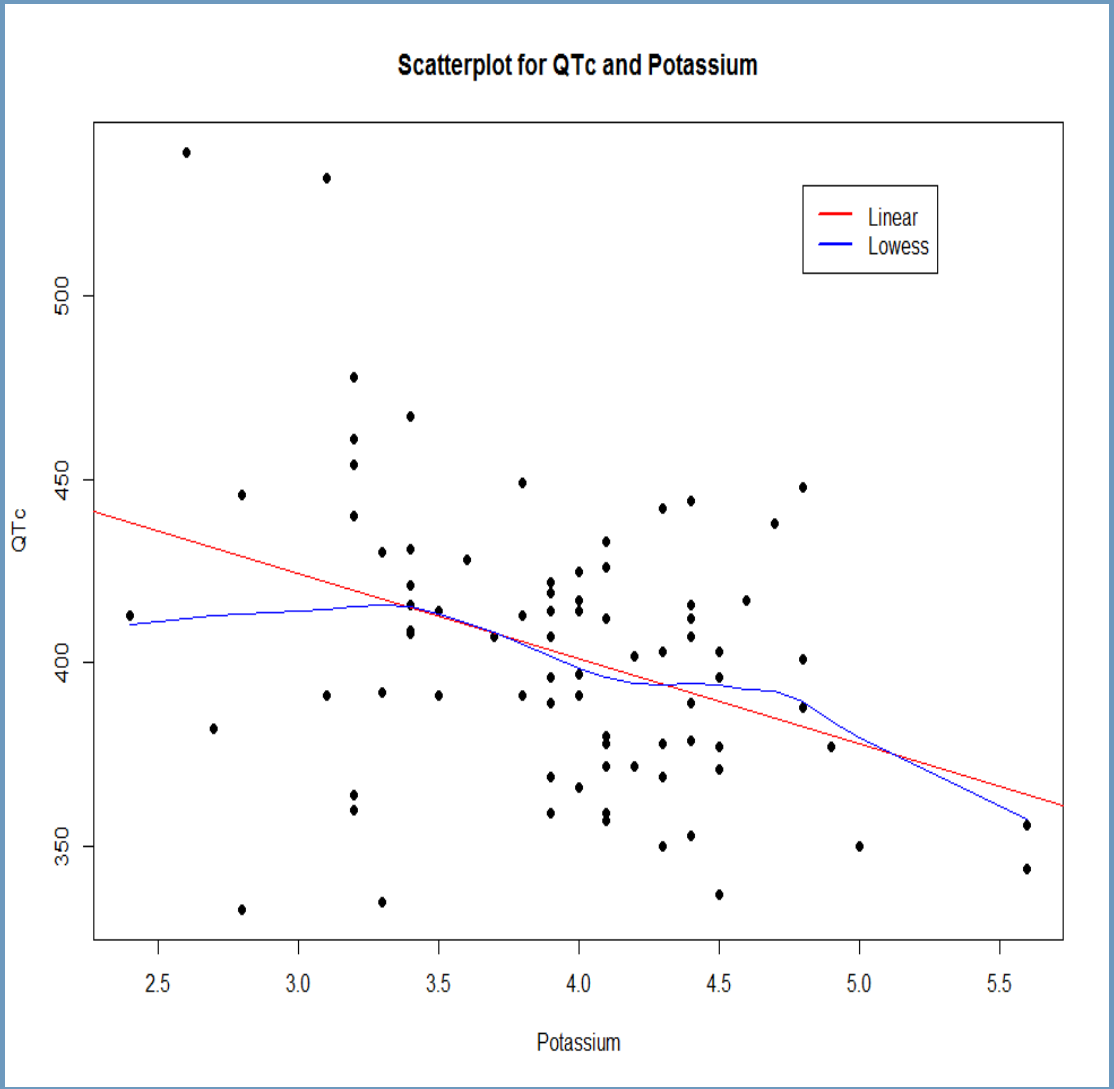
QTc vs Methadone (mg/kg/dose)



p = 0.51

Madden K, et. al. (2017). Pediatric Blood & Cancer, 64(11), e26614.

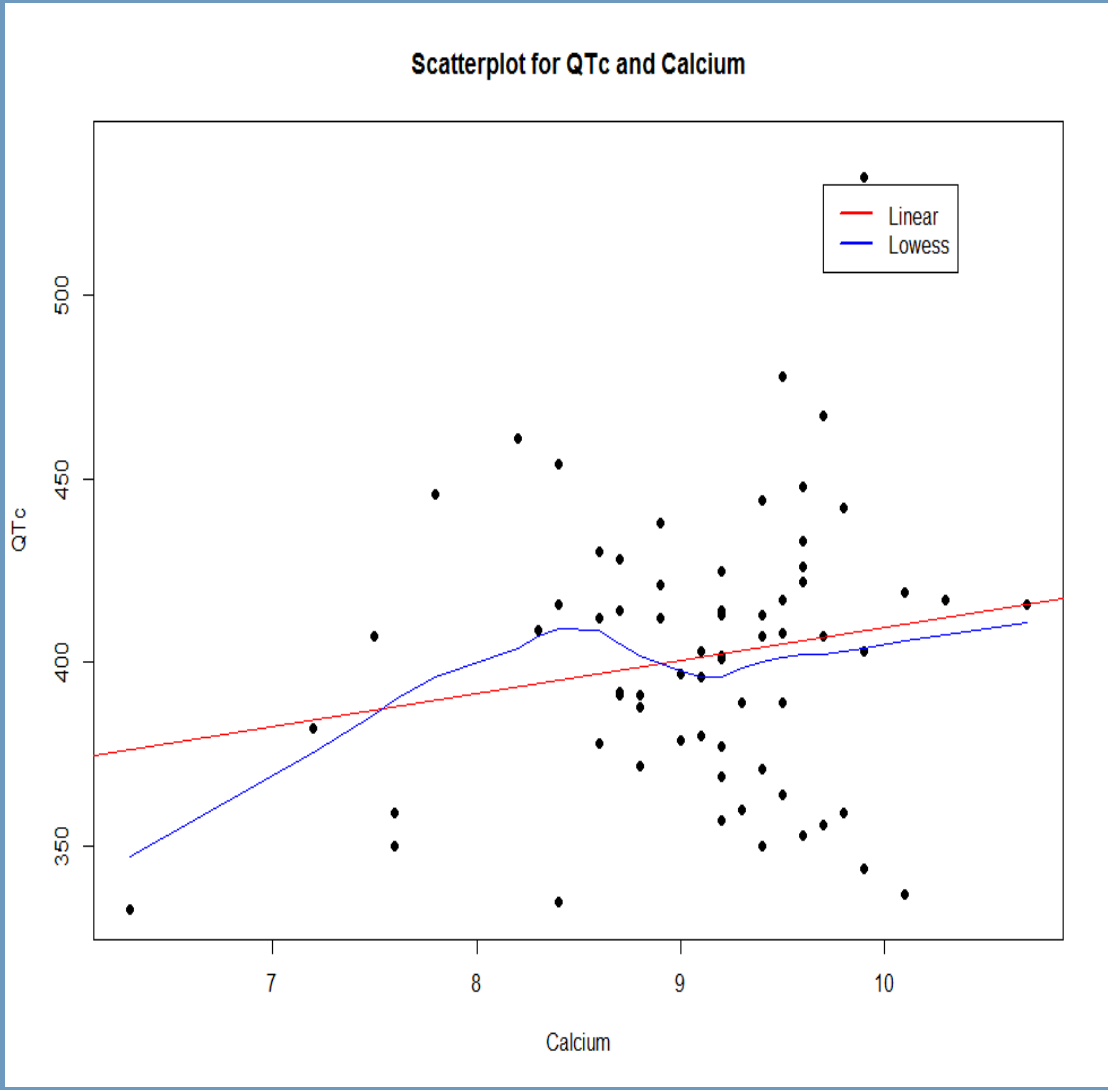
QTc vs Potassium



p = 0.04

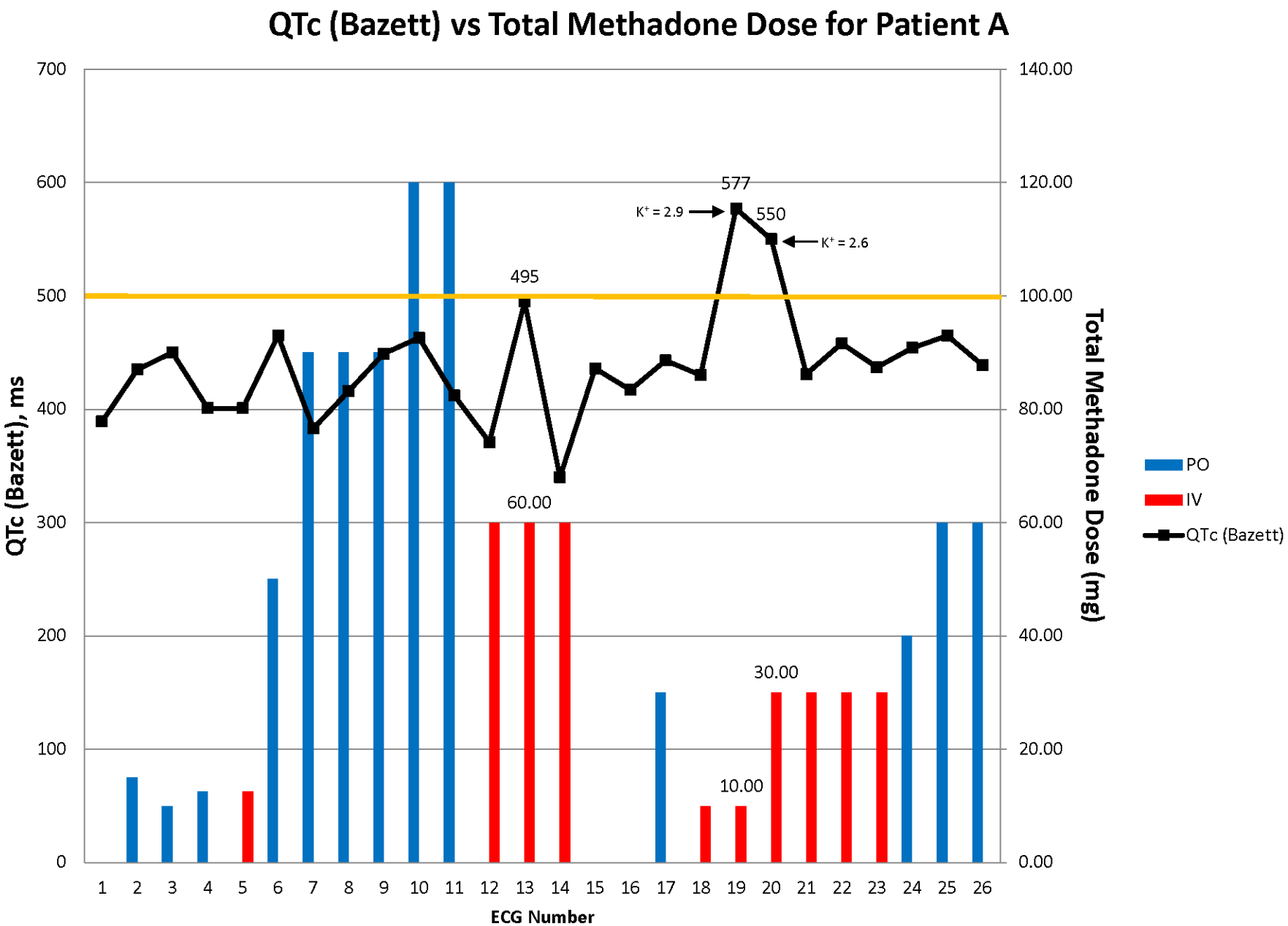
Madden K, et. al. (2017). Pediatric Blood & Cancer, 64(11), e26614.

QTc vs Calcium Level



p = 0.01

Madden K, et. al. (2017). Pediatric Blood & Cancer, 64(11), e26614.



Madden K, et. al. (2017). Pediatric Blood & Cancer, 64(11), e26614.

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

Madden K., et. al. (2019). Journal of Pain and Symptom Management, 2019 Jun 11.

Methods

- Electrocardiogram
  - Baseline = within 1 month of starting methadone
  - 1-2 weeks after starting methadone
  - 4-6 weeks after starting methadone
  - QTc machine calculated
  - QTc manually calculated

Madden K., et. al. (2019). Journal of Pain and Symptom Management, 2019 Jun 11.

What did we find?

Table 2. Longitudinal QTc interval assessments at baseline, 1-2 weeks, and 4-6 weeks

	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)	

[a] Comparison of QTc at Baseline vs 1-2 weeks (Wilcoxon signed rank test)
[b] Comparison of QTc at Baseline vs 4-6 weeks (Wilcoxon signed rank test)
[c] Upper limit of normal for: pre-pubertal children = 460 ms; pubertal males = 470 ms; pubertal females = 480 ms

Madden K., et. al. (2019). Journal of Pain and Symptom Management, 2019 Jun 11.

Other results

Table 3. Known Risk Factors for QTc Prolongation

	1-2 weeks n = 38	4-6 weeks n = 31	*P*-value
Number (%) of patients on medications that:			
Directly increase QTc	33 (87%)	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]

[a] One unit decrease of potassium (mEq/L) was significantly correlated with a 17 msec increase in the QTc

Madden K., et. al. (2019). Journal of Pain and Symptom Management, 2019 Jun 11.

Methadone as the Initial Long-Acting Opioid in Children with Advanced Cancer

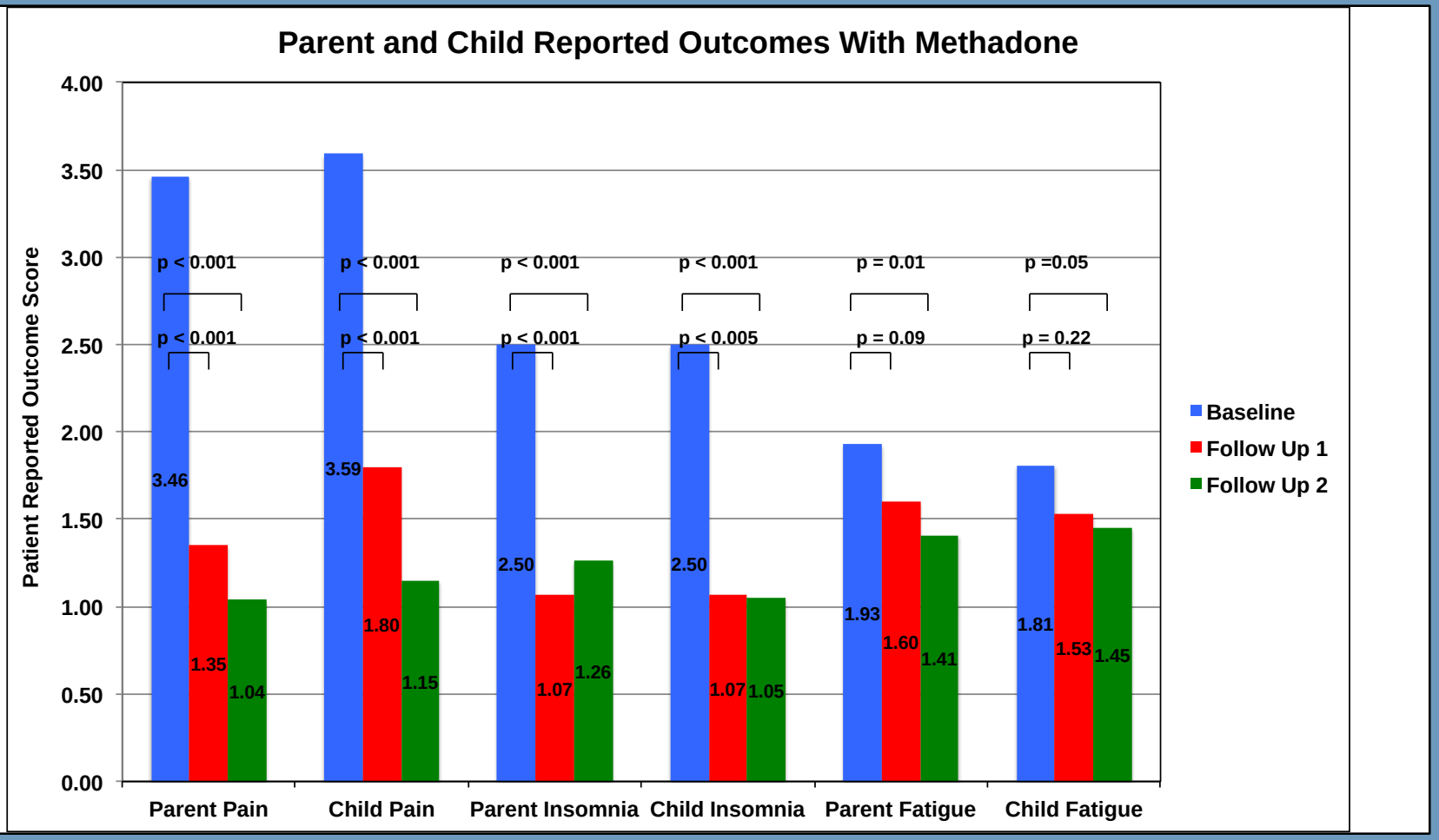
Madden K, et. al. (2018). Journal of Palliative Medicine, 21(9), 1317-1321.

Background

- Pain is the most common symptom reported by children with advanced cancer
- Children cannot reliably swallow tablets until 7 or 8 years of age
- This severely restricts the use of long-acting opioids in these children except for:
  - Fentanyl transdermal patch – little subcutaneous fat means less absorption
  - **Methadone – only long-acting opioid that is a liquid**

Madden K, et. al. (2018). Journal of Palliative Medicine, 21(9), 1317-1321.

What did we find?



Madden K, et. al. (2018). Journal of Palliative Medicine, 21(9), 1317-1321.

Other results

79% needed NO CHANGE in dose

17% needed a decrease in dose

4% needed an increase in dose

Madden K, et. al. (2018). Journal of Palliative Medicine, 21(9), 1317-1321.

Other results

- No opioid-induced neurotoxicities or cardiac arrhythmias were detected
- No standard protocol for follow-up ECG, but a majority (38/47 [81%]) of patients had one ECG during the study period
  - None of these patients demonstrated prolongation of the QTc interval

Madden K, et. al. (2018). Journal of Palliative Medicine, 21(9), 1317-1321.

Other results

- No significant improvement in psychological scores of nervousness, sadness, or irritability as pain, insomnia, and fatigue improved

Madden K, et. al. (2018). Journal of Palliative Medicine, 21(9), 1317-1321.

Methadone as the first long-acting opioid in children with cancer

- Conclusions:
  - Methadone as the first long-acting opioid in children with advanced cancer is both effective and safe
  - As pain improved, sleep disturbances and fatigue also improved
  - The severity of the psychological symptoms at baseline was low and so the margin for clinically significant improvement in these scores may be limited

Madden K, et. al. (2018). Journal of Palliative Medicine, 21(9), 1317-1321.

Clinically Significant Drug-Drug Interaction Between Methadone and Cannabidiol (CBD)

Madden K, et. al. (2020). Pediatrics. Jun 1;145(60.

Clinically Significant Drug-Drug Interaction Between Methadone and Cannabidiol (CBD)

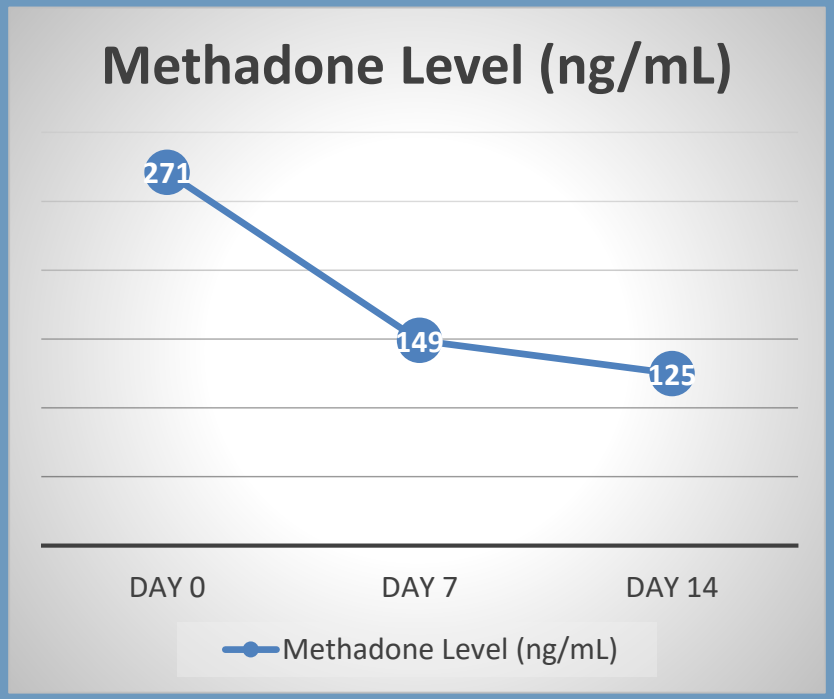
- Neuroendocrine tumor with metastatic disease to the liver, lungs, thoracic vertebrae, and scattered lesions in the cerebral cortex
- Nociceptive pain was primarily in the upper thoracic spine and neuropathic components manifested as sharp, radiating pain into the lower thoracic spine and sacrum
- Pain controlled with methadone 7.5 mg po BID and morphine 7.5 mg po q4 hours prn breakthrough pain
- Typically used 1 to 2 breakthrough doses of morphine a few times per week
- She had been on this regimen for ~4 months, and during that time, she never exhibited any significant opioid-related side effects, including hallucinations, myoclonus, or excessive drowsiness

Clinically Significant Drug-Drug Interaction Between Methadone and Cannabidiol (CBD)

- Increased fatigue and sleepiness, which were markedly worse than baseline
- No recent changes to prescribed medications
- ROS: No fever, rhinorrhea, cough, neck pain, photophobia, tonic-clonic activity, staring episodes, hallucinations, altered mental status, and ill contacts
- CT and MRI head – no changes, EEG no seizure activity
- Labs nml
- Pertinent PE:
  - Fatigued, pupils 2 mm and minimally reactive.
  - She was alert and oriented to person, place, and time with no delirium (Cornell Assessment of Pediatric Delirium score of 0)
  - Cranial nerves 2 through 12 were intact. She had normal strength with no sensory deficit, the Romberg sign was negative with no dysmetria, and her gait was normal.

Clinically Significant Drug-Drug Interaction Between Methadone and Cannabidiol (CBD)

- Initial serum methadone level was 271 ng/mL
- 7 days after stopping cannabidiol:
  - Methadone level was 149 ng/mL
  - Pupils were 3 mm and mildly reactive
  - Self-reported fatigue level of 2 out of 4
- 14 days after stopping cannabidiol:
  - Methadone level was 125 ng/mL
  - Pupils were 3 mm and briskly reactive
  - Self-reported fatigue level of 1 out of 4



Drug Interactions

- Methadone is metabolized by:
  - CYP3A4
  - CYP2C19
  - CYP2D6
  - CYP1A2

Clinically Significant Drug-Drug Interaction Between Methadone and Cannabidiol (CBD)

- Methadone is metabolized by the CYP3A4 and CYP2C19 enzyme system
- Blocking this pathway would lead to increased serum methadone levels
- Cannabidiol is both metabolized by ***and inhibits*** CYP3A4 and CYP2C19

Very-Low-Dose Methadone To Treat Refractory Neuropathic Pain in Children with Cancer

Madden K, & Bruera E. (2017). Journal of Palliative Medicine, 20(11), 1280-1283.

Case #1

- Reason for Consult: Insomnia
- HPI
  - BN is an almost 20-month-old male with infantile ALL
  - Care was transferred to MD Anderson for further disease-directed therapies
  - Supportive Care consulted for insomnia

Madden K, & Bruera E. (2017). Journal of Palliative Medicine, 20(11), 1280-1283.

Case #1

- Since diagnosis at 4 months of age he has never slept through the night

- His parents attribute this to:
  - His young age
  - Chronic medical condition
  - Frequent hospitalizations with frequent interruptions of sleep

- They have tried:
  - Behavioral/environmental modification with establishment of consistent routine
  - Pharmacologically, they have tried without success:
    - Melatonin
    - Lorazepam
    - Diphenhydramine (caused a paradoxical reaction)

Madden K, & Bruera E. (2017). Journal of Palliative Medicine, 20(11), 1280-1283.

Case #1

- Developmental Hx
  - Gross Motor – pulls to stand, walking OK, does not run = mild delay
  - Fine Motor – scribbles but cannot build block tower = mild delay
  - Language – 2-3 words = mild delay
  - Social – helps in house, can use fork = normal

Madden K, & Bruera E. (2017). Journal of Palliative Medicine, 20(11), 1280-1283.

Case #1

- Assessment/Plan

- Insomnia, etiology uncertain.
  - Start olanzapine 0.7 mg (0.05 mg/kg/dose) p.o. at bedtime and they may repeat this dose one time during the night should he awaken.

Madden K, & Bruera E. (2017). Journal of Palliative Medicine, 20(11), 1280-1283.

Case #1

- Olanzapine did not help, even with increasing doses up to 0.1 mg/kg/dose.

- Parents recall BN being on amitriptyline 2.5 mg (0.2 mg/kg per dose) at bedtime prescribed by a physician in Corpus Christi but uncertain why
  - Maybe neuropathic pain?
- Father does not think it helped with sleep, while his mother thought it did

Madden K, & Bruera E. (2017). Journal of Palliative Medicine, 20(11), 1280-1283.

Case #1

- Upon more questioning about sleep, his mother reports that he seems to have extreme sensitivity in his bilateral lower extremities and feet, not wanting any full length pajamas, socks, sheets or blankets on his legs or feet when he sleeps. This does not seem to be the case during the day but…

Madden K, & Bruera E. (2017). Journal of Palliative Medicine, 20(11), 1280-1283.

Case #1

- …during physical therapy (remember, he has some gross motor delay) it is noted that he pulls to stand but will often off-load his weight by holding on to table and pressing up. Also, when crawling he will occasionally have his right wrist "give out" and cry as if in pain.

Madden K, & Bruera E. (2017). Journal of Palliative Medicine, 20(11), 1280-1283.

Case #1

- Change thinking to refractory neuropathic pain (was on maximal doses of gabapentin) we start amitriptyline at previous dose of 0.2 mg/kg/dose
- No effect so increase dose to 0.5 mg/kg/dose
- No effect

Madden K, & Bruera E. (2017). Journal of Palliative Medicine, 20(11), 1280-1283.

Case #1

- We are getting stuck…
- How about methadone?
- What is “very-low-dose” methadone?
  - Arbitrary definition
  - < 50% of normal starting dose (0.1 mg/kg/dose q12 hours)

Madden K, & Bruera E. (2017). Journal of Palliative Medicine, 20(11), 1280-1283.

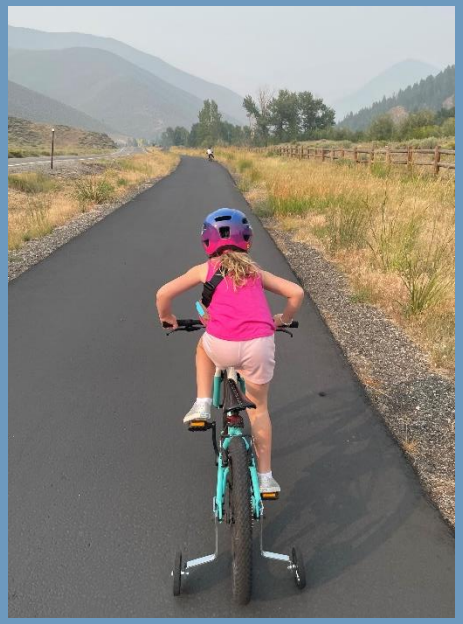
Case #1

- Start methadone 0.3 mg q12 hours (0.03 mg/kg/dose q12 hours)
- Within 3 days, his appetite increased significantly
- Within 5 days, he went from pulling to stand to walking without assistance
- Within 7 days, he began sleeping through the night

Madden K, & Bruera E. (2017). Journal of Palliative Medicine, 20(11), 1280-1283.

In the absence of data, all opinions are equal.

deuter
CAMELBAK



Bibliography

1. Madden K, Park M, Liu D, Bruera E. The frequency of QTc prolongation among pediatric and young adult patients receiving methadone for cancer pain. Pediatric blood & cancer. 2017 Nov;64(11):e26614.
2. Madden K, Bruera E. Very-low-dose methadone to treat refractory neuropathic pain in children with cancer. Journal of palliative medicine. 2017 Nov 1;20(11):1280-3.
3. Madden K, Mills S, Dibaj S, Williams JL, Liu D, Bruera E. Methadone as the initial long-acting opioid in children with advanced cancer. Journal of palliative medicine. 2018 Sep 1;21(9):1317-21.
4. 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. Journal of palliative medicine. 2018 Oct 1;21(10):1408-13.
5. 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. Journal of pain and symptom management. 2019 Feb 1;57(2):260-5.
6. Madden K, Jo E, Williams JL, Liu D, Bruera E. Corrected QT Interval Prolongation in Pediatric and Young Adult Patients on Methadone for Cancer Related Pain. Journal of pain and symptom management. 2019 Jun 11.
7. Madden K, Tanco K, Bruera E. Clinically Significant Drug-Drug Interaction Between Methadone and Cannabidiol. Pediatrics. 2020 Jun 1;145(6).

Research – It's a Team Sport

- **MD Anderson Palliative Care**
  - Dr. Eduardo Bruera
  - Dr. Joseph Arthur
  - Dr. Ashan Azhar
  - Dr. Shalini Dalal
  - Dr. Maxine De La Cruz
  - Dr. Marvin Delgado Guay
  - Dr. Rony Dev
  - Dr. Daniel Epner
  - Dr. Ali Haider
  - Dr. Yvonne Heung
  - Dr. David Hui
  - Dr. Sarah Mills
  - Dr. Akhila Reddy
  - Dr. Suresh Reddy
  - Dr. Ishwaria Subbiah
  - Dr. Kimberson Tanco
  - Dr. Marieberta Vidal
  - Dr. Paul Walker
  - Dr. Angelique Wong
  - Dr. Sriram Yennu
  - Dr. Donna Zhukovsky

- **Biostatistics**
  - Diane Liu
  - Dr. Shiva Dibaj
  - Eunji Jo
  - Minjeong Park

- **PC Research Team**
  - Vera De La Cruz
  - Janet Williams
  - Allison De La Rosa
  - Sneha Joshi
  - Joseph Chen
  - Yvette Ross

Contact Info:
kmadden@mdanderson.org
@madden_kevin