Management of Methadone Dosing in Hospitalized Patients

With a focus on abnormal QTc on EKG

MIA SORCINELLI, MD, FASAM

Learning Objectives

- Briefly review Opioid Use Disorder Scope and treatment
  - Glimpse inside the world of Methadone clinics
- Discuss literature and expert opinion guidance around QTc prolongation
- Demonstrate common scenarios that lead to abnormal EKG--QTc
- Weigh risks of abnormal QTc against risks of opiate use disorder worsening
- Develop problem-solving strategy for managing abnormal EKGs in patients on methadone

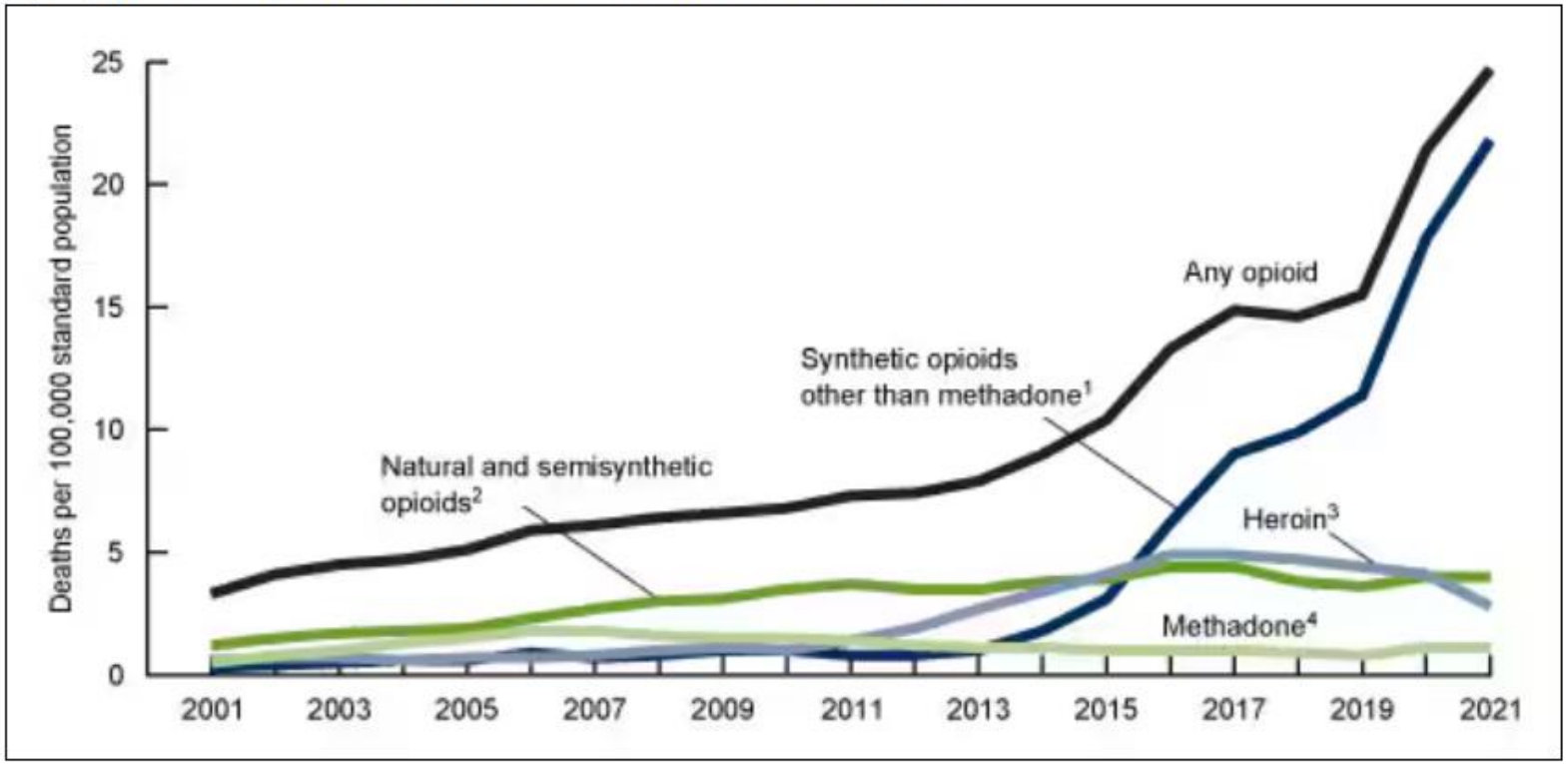
Disclaimers

- I'm not a cardiologist!
- I work for Spectrum Health Systems—they operate methadone clinics around the state including in Haverhill. I mainly work at their site in Saugus

Inspiration for this talk

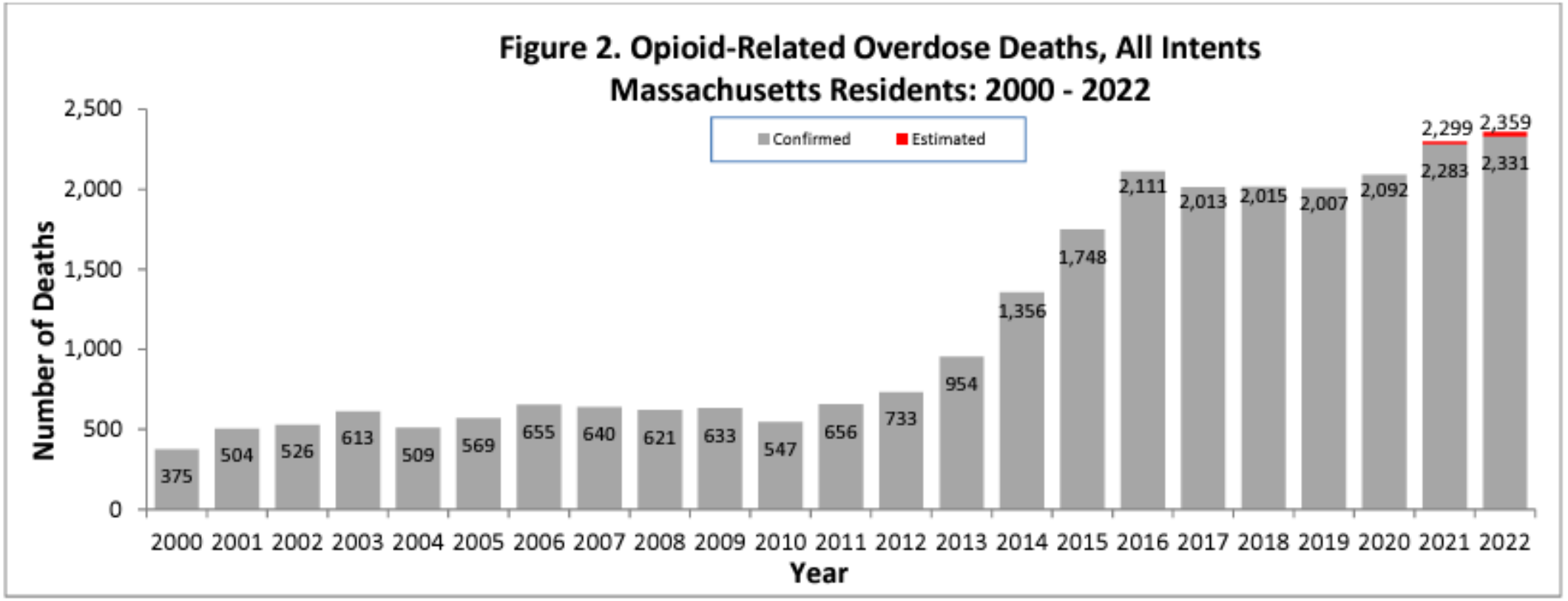
CDC: Overdose deaths Opioids

Figure 4. Age-adjusted rate of drug overdose deaths involving opioids, by type of opioid: United States, 2001–2021



Source: CDC Data Briefs
https://www.cdc.gov/nchs/products/databriefs/db457.htm#fig2

Massachusetts Overdose Deaths

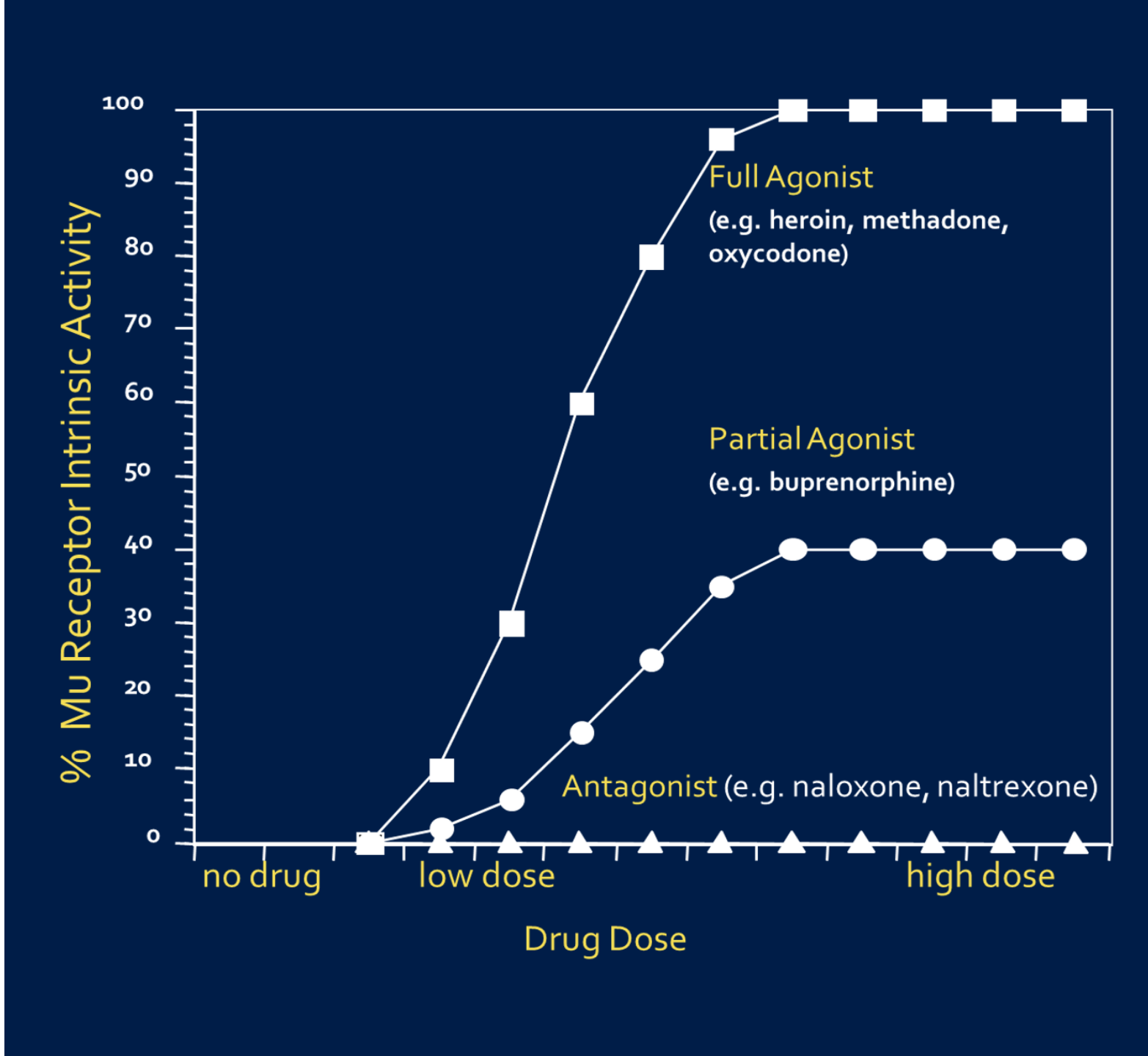


Source: mass.gov current overdose data Dec 2023

Treatment Works

- There are three medications approved by the FDA for treatment of Opioid Use Disorder
  - Methadone -- Oral liquid -- only dispensed from Outpatient Treatment Program (OTP), not able to be prescribed from office setting by PCPs, etc.
  - Buprenorphine (aka Suboxone/Zubsolv/Sublocade/Subutex) – requires minimal training or online application to prescribe in an office setting
  - Vivitrol (Naltrexone IM) – injection – every 28 days

Opioid Agonists and Antagonists



Methadone

- Developed in 1940s
- Very long acting synthetic opiate
- FULL AGONIST to the opiate receptor
- Most effective in terms of treatment retention of the 3 treatment options—about 85% of patients stay in treatment
- Strict federal laws govern its use
- Dispensed from Methadone clinics—very separate from primary care, etc

Methadone

- Admission to methadone program usually includes a standardized intake with the admission department (in Mass there are specific forms required by Board of Substance Abuse Services and Dept Public Health)
- Nursing assessment including urine drug screen, COWS score, breathalyzer
- Physician or NP/PA assessment comprised of a focused H&P to gauge eligibility for methadone maintenance and elucidate any safety issues prior to first dose
- Newly updated rules as of April 2, 2024 give admitting physician/NP broader dosing ranges based on tolerance/medical risk
- Prior first day max was 30 mg at one time with 10 mg extra (40 total)
- Induction Period: first 10 days

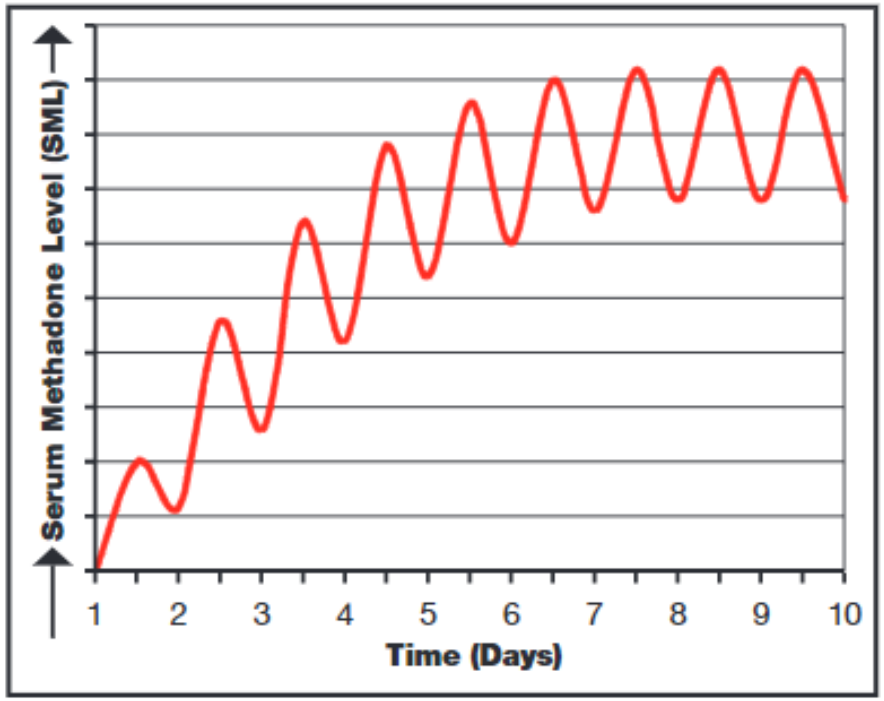
Methadone

- Evidence shows that daily doses over 60 mg increase retention in treatment and cut down on illicit use (dose dependent)
- Across all clinics in the country, average methadone dose is somewhere between 80-120 mg daily
- Most patients have a “stable dose” at which they experience alleviation of their cravings, often this dose is described by patient as “blocking dose”
- Methadone has a very long half life and so each day’s serum level includes some of the previous day’s dose—adjust slowly in patients new to treatment

Methadone

Figure 1: Steady-state methadone concentration reached in about 5 days.

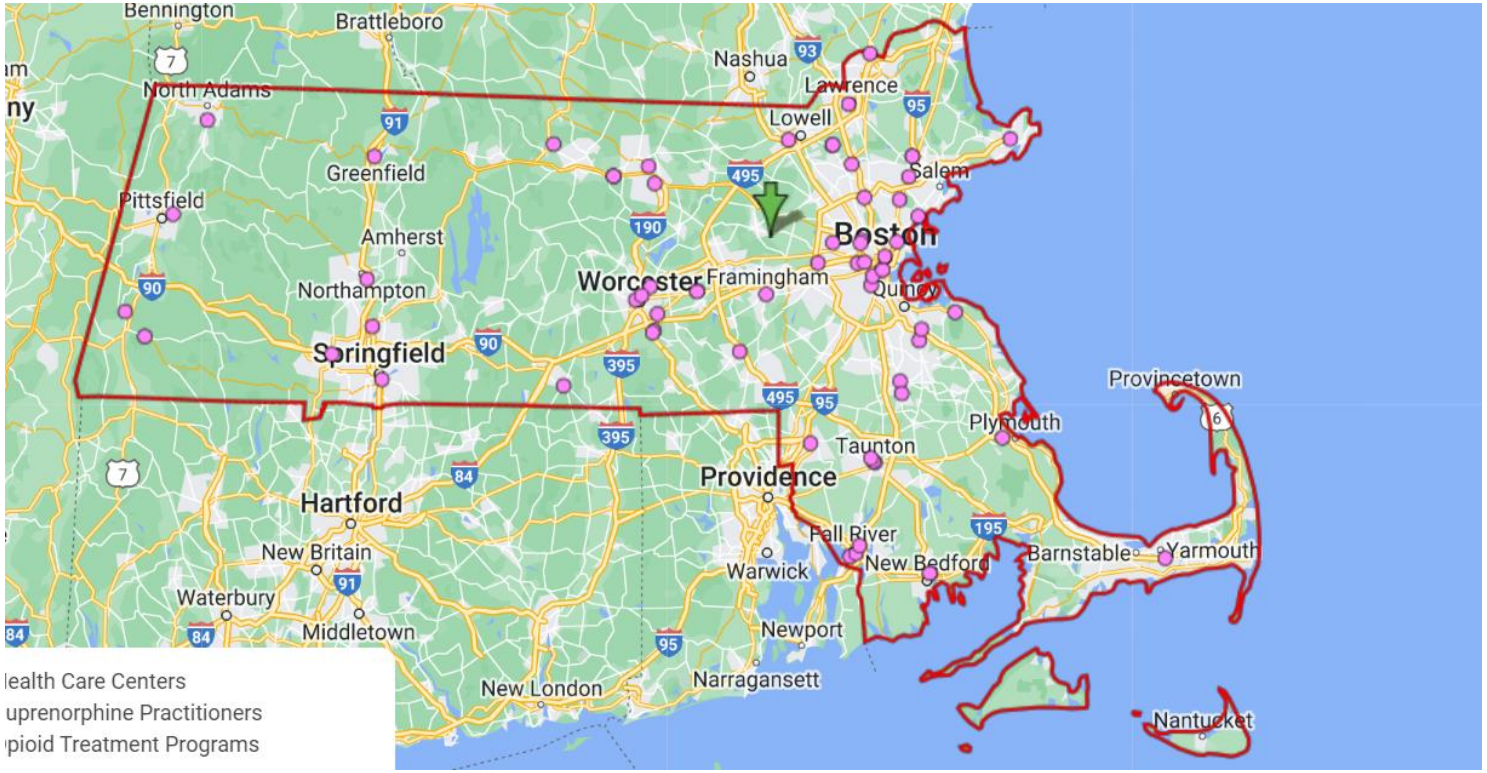
Adapted from Payte 2002.



Methadone Benefits

- **Methadone is a life-saving medication**
- The disease of Opioid Use Disorder is severe and life threatening
- Methadone decreases IV drug use, overall drug use, rates of HIV and HCV, as well as illicit activities (theft, sex work, etc)
- Long term treatment is more effective than short term, some data says 2 years at a minimum

Methadone clinics exist across MA



Source:
https://findtreatment.gov/
Run by Samhsa
Filterable map and list

Methadone adverse effects

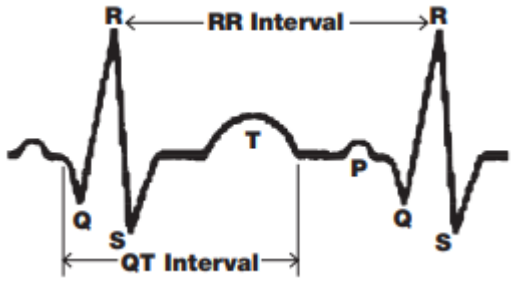
- **Serious Reactions:** respiratory depression, apnea, respiratory arrest, central sleep apnea, hypotension, severe, shock, cardiac arrest, **QT prolongation, torsades de pointes, arrhythmia, ventricular tachycardia, ventricular fibrillation**, cardiomyopathy, bradycardia, seizures, paralytic ileus, biliary spasm, ICP incr., pulmonary edema, dependency, abuse, hypersensitivity rxn, anaphylaxis, adrenal insufficiency, opioid-induced androgen deficiency, withdrawal sx if abrupt D/C

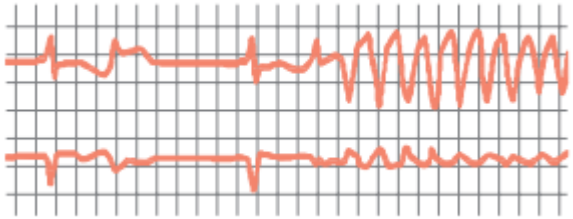
Methadone metabolism

- Methadone metabolized (mainly) by the CYP450 3A4 and 2B6
- **Multiple** substances interact with methadone metabolism in the body
  - Benzodiazepines metabolized by same pathway➔ increases effect of both
  - Phenobarbital➔ decrease methadone levels
  - Erythromycin, Seroquel, celexa, etc etc etc ➔ prolonged QTc

- If you have a patient on methadone, add it to their medication list (<u>does not show up in the PMP if dispensed from a methadone clinic</u>)
  - Consider carefully new meds and weigh risk/benefit

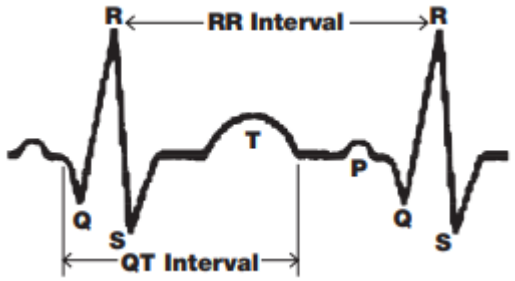
QTc Prolongation

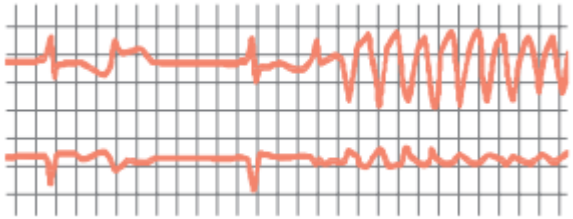




- We measure the QT interval and use the QTc (corrected for heart rate)
  - Ok to trust the machine for this calculation in general
- Normal for men is below 440/450 and women below 460/470
- Some consider > 500 a cutoff for more concern
- Pathophysiology is complicated
  - Abnormalities in voltage-gated potassium channels have been shown to lead to prolonged action potentials that are expressed as long Q-T intervals
  - Methadone has been found to interact with the voltage-gated potassium channels of the myocardium
  - Genetic component increases risk (Familial Long QT Syndrome)
- Can result in Torsade De Points which can cause fainting, V Tach, more rarely death

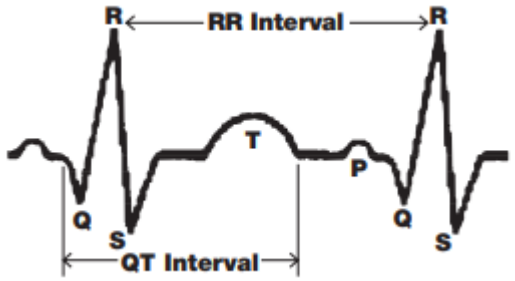
QTc Prolongation

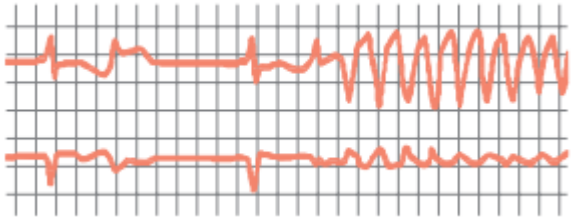




- What I say to patients is "Methadone can sometimes cause a pause or a slowing in part of your heart rhythm. This can potentially lead to a dangerous heart rhythm. I can't hear it with my stethoscope and you can't feel it. The only way to monitor it is to get an EKG that I will review."

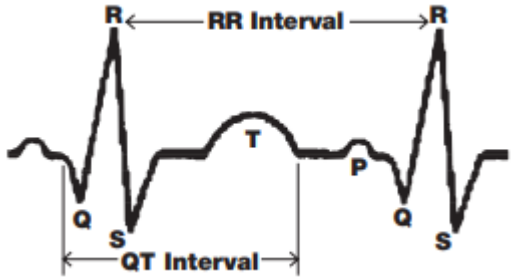
QTc Prolongation

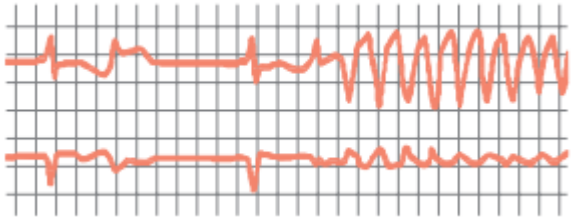




- Known risk factors:
  - Female sex
  - Hypokalemia
  - High-dose methadone
  - Drug interactions
  - Underlying cardiac conditions
  - Unrecognized congenital long Q-T interval syndrome
  - Predisposing DNA polymorphisms

QTc Prolongation: Incidence





- Small Study: Inner city urban community (Bronx, New York) that has a large number of patients on methadone.
  - Telemetry records, nursing documentation and electronic charts of 291 patients spanning 856 encounters were evaluated
  - QT was manually measured from ECG, QTc >470 ms in males and >480 ms in females was considered to be prolonged.
  - Patients had prolonged QTc 25.6% of encounters
  - QTc >500 ms 14.1% of encounters
  - **Ventricular arrhythmias 3.4% of encounters**
  - There was a very weak dose dependent relationship between methadone dose and QTc
  - Patients were on at least one QT prolonging drugs during 39% of the encounters
  - Patients who were receiving two interacting drugs in addition to methadone had the highest prevalence (29%) of QTc prolongation.

Chowdhury M, Wong J, Cheng A, Khilkin M, Palma E. Methadone Therapy in Underserved Urban Community: QTc Prolongation and Life-Threatening Ventricular Arrhythmias. Cardiovasc Ther. 2015 Jun;33(3):127-33.

Further evidence?

- 2013 Cochrane Review—insufficient evidence to support EKG screening for prolonged QTc for all patients on methadone.
  - Pani PP, Trogu E, Maremmani I, Pacini M. QTc interval screening for cardiac risk in methadone treatment of opioid dependence. Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD008939.

- "Methadone is associated with QTc prolongation in a nonclinically significant dose-related manner. **Cardiac events were rare and the sudden cardiac death rate was below that of the general population.** Current recommendations for cardiac risk assessment in methadone-maintained patients should be reconsidered."
  - Bart G, Wyman Z, Wang Q, Hodges JS, Karim R, Bart BA. Methadone and the QTc Interval: Paucity of Clinically Significant Factors in a Retrospective Cohort. **J Addict Med. 2017** Nov/Dec;11(6):489-493.

Case 1: “High” dose methadone

- Patient is a 37 yo woman with a 20 year history of Opioid Use Disorder, started using Percocet after wisdom tooth extraction and rapidly escalated to IV heroin use
  - Has tried 15 detox programs
  - Has had 7 overdoses requiring narcan/ER visits
  - Has tried Suboxone program at local FQHC 2 times without attaining sobriety
  - Has been on Methadone at local clinic for 3 years and has completely stopped using illicit opiates, has a job and is successfully parenting her 1 year old child
  - Current dose is 140 mg daily

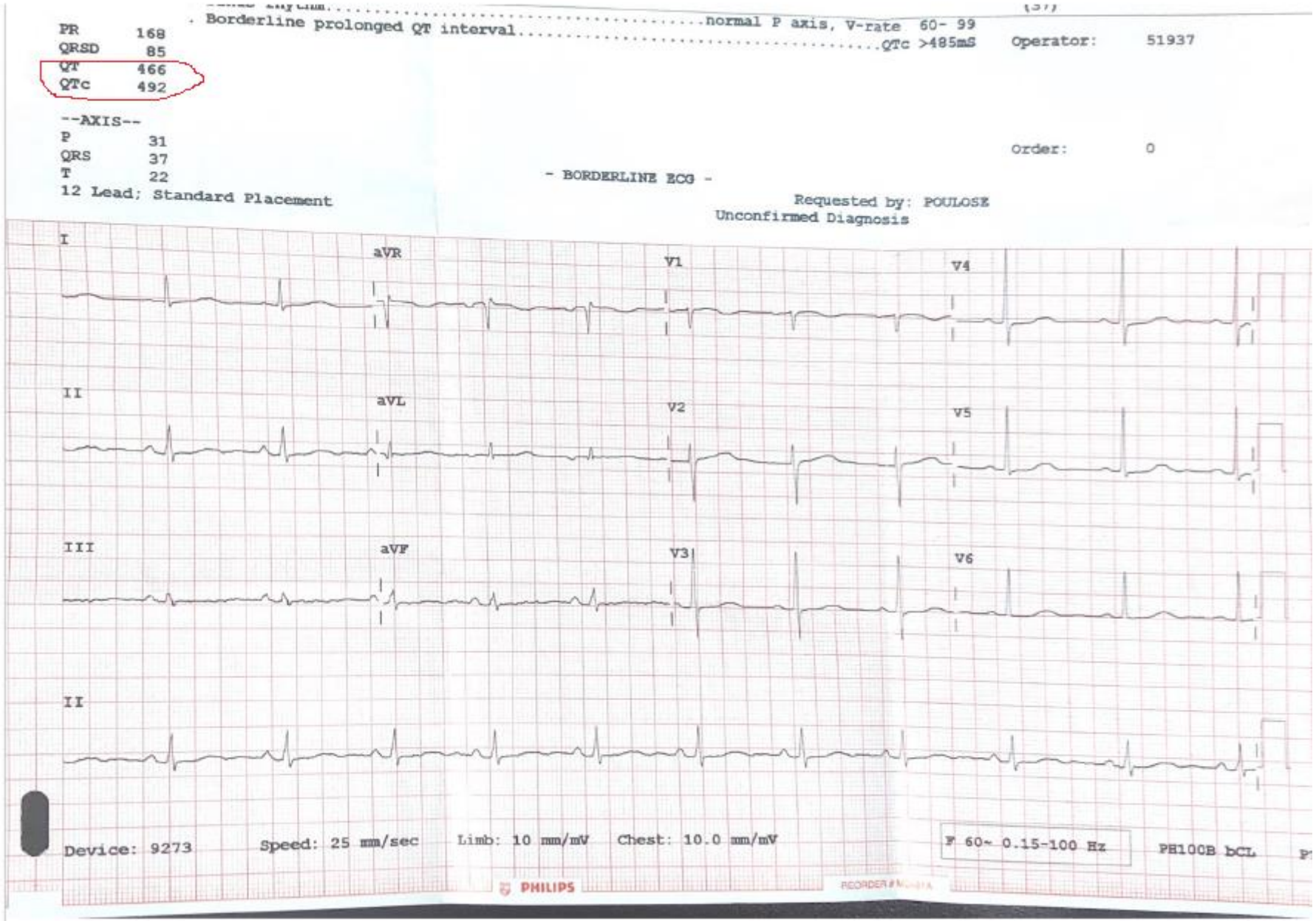
Case 1: "High" dose methadone

- Patient is a 37 yo woman with a 20 year history of Opioid Use Disorder
  - Has tried 15 detox programs
  - Has had 7 overdoses requiring narcan/ER visits
  - Has tried Suboxone program at local FQHC 2 times without attaining sobriety
  - Has been on Methadone at local clinic for 3 years and has completely stopped using illicit opiates, has a job and is successfully parenting her 1 year old child
  - Current dose is 140 mg daily

Case 1: “High” dose methadone

- She has had 3 days of viral gastroenteritis and presents to the ER after being unable to tolerate any PO today and feeling weak
- VS: HR 100, BP 97/65, RR 20
- An EKG is obtained

Case


. Borderline prolonged QT interval
normal P axis, V-rate 60- 99
QTc >485mS
Operator: 51937
PR 168
QRSD 85
QT 466
QTc 492
--AXIS--
P 31
QRS 37
T 22
12 Lead; Standard Placement
Order: 0
- BORDERLINE ECG -
Requested by: POULOSE
Unconfirmed Diagnosis
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II
Device: 9273
Speed: 25 mm/sec
Limb: 10 mm/mV
Chest: 10.0 mm/mV
F 60~ 0.15-100 Hz
PH100B bCL
PHILIPS

Case 1: “High” dose methadone

- What now?

Case 1: “High” dose methadone

- What now?

- Some choices:
  - Decrease methadone dose by 50 mg?
  - Decrease methadone dose by 10% (or more?)
  - Check electrolytes
  - Nothing

Discuss:

Case 1: “High” dose methadone

- What about IV methadone if she is vomiting?
  - Just to file away: IV methadone is an option, I would reserve it for only the most serious situations where someone can absolutely NOT tolerate oral
  - IV methadone contains chlorobutanol and this increases risk of QT prolongation

Case 1: “High” dose methadone

- BMP shows her K is 3
- IVF given
- KCl given IV
- Repeat EKG in 4 hours shows her QTc is now 430ms

Case 2: Murkier Waters…

- Pt is a 67 yo gentleman with a 20+ year hx of OUD, has been on methadone for years.
  - CD is 80 mg, pt not using illicit opiates, feels good at current dose
  - PMHx notable for hx of CAD with stenting, tobacco use disorder
  - intellectual disability and poor insight into overall health
- Seen at urgent care yesterday with cough, given azithromycin and prednisone for "COPD exacerbation"

Case 2: Murkier Waters…

- Pt arrives in the ER with somewhat atypical chest pain
- VSS: HR 70s, BP 130/80, RR 16, O2 97%
- EKG is performed
- First Troponin comes back normal

Loc: 26

Q-T/Q-Tc	514/543	ms	
P-R-T axes	-1	-32	61

Prolonged QT
Abnormal ECG

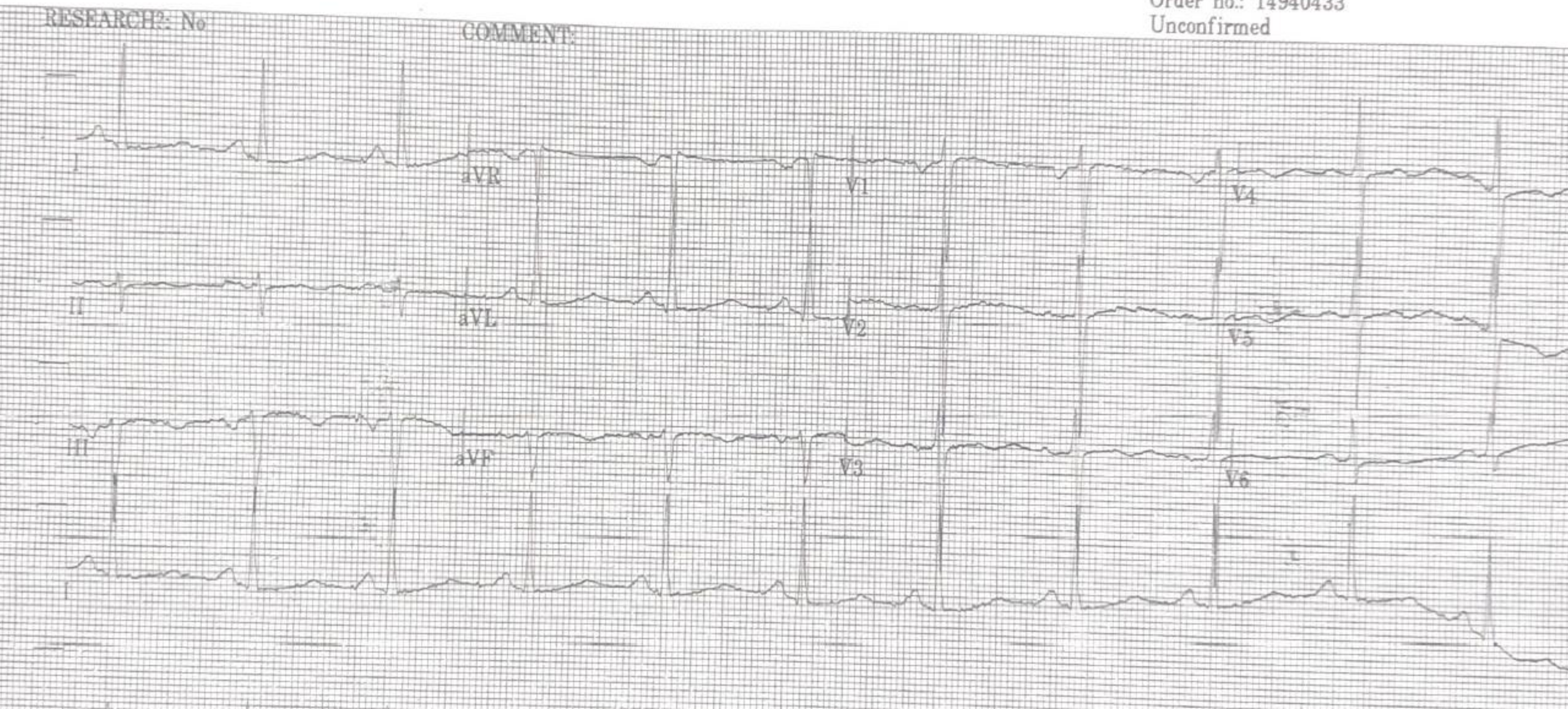
Technician: TEVANS1

Visit: 0722373-20220314

Order no.: 14940433
Unconfirmed

RESEARCH?: No

COMMENT:



Case 2: Murkier Waters…

- Pt's cardiologist speaks with the ER physician and wants to admit the patient to telemetry and r/o MI
- What to do now with the methadone dose 80 mg and QTc of 540?

Case 2: Murkier Waters…

Some choices:

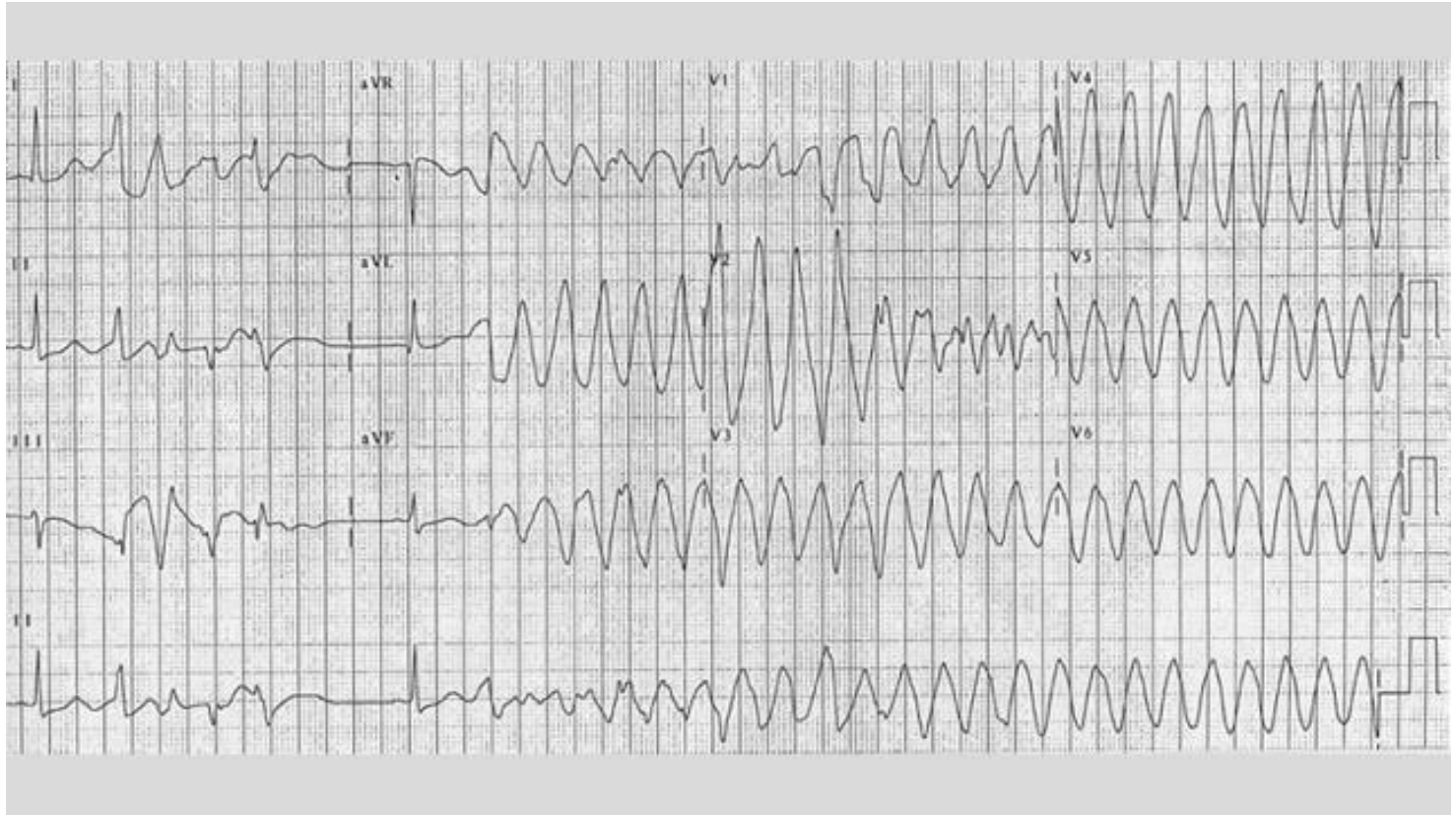
- Decrease methadone dose by 50 mg
- Decrease methadone dose by 10%
- Check electrolytes
- Medication reconciliation?
- Nothing

Discuss:

Case 2: Murkier Waters…

- Telemetry nurse calls rapid response

Case 2: Murkier Waters…



Case 2: Murkier Waters…

- NOW WHAT?

Case 2: Murkier Waters…

- NOW WHAT?
  - Call a code, ACLS, save his life with electricity, etc.

Management steps

- Is the patient **unstable**? Follow ACLS algorithms.
- Is the patient stable with an abnormal QTc?
  - Telemetry reasonable if other cardiac history
  - Medication reconciliation (remember the study showing 39% of patients on another med that can prolong QTc)
  - Electrolyte repletion—focus on normalizing K
  - Repeat the EKG after electrolyte repletion
  - If at that point the QTc is still >500 can consider adjustment to methadone dose

Adjusting Methadone doses

- If a patient skips a day (or even two or more) they will still have methadone in their system—slow on, slow off.
- In the outpatient setting we tend to adjust based on percent of the current dose—usually don't increase by more than 10-20% of current dose
- Usually don't decrease by more than 10-20% of current dose
- Assess stability of patient on current dose
- Have a shared decision-making conversation with the patient if they are stable

Massachusetts Consultation Service

MCSTAP

for Treatment of Addiction and Pain

Call **1-833-PAIN-SUD** (1-833-724-6783)

Monday through Friday - 9 am to 5 pm

WWW.MCSTAP.COM

mcstap@beaconhealthoptions.com Christopher.Shanahan@bmc.org;
Amy.Rosenstein@beaconhealthoptions.com; John.Straus@beaconhealthoptions.com

Massachusetts Consultation Service
MCSTAP
for Treatment of Addiction and Pain

Educational Resources

Bibliography

Bart G, Wyman Z, Wang Q, Hodges JS, Karim R, Bart BA. Methadone and the QTc Interval: Paucity of Clinically Significant Factors in a Retrospective Cohort. J Addict Med. 2017 Nov/Dec;11(6):489-493

Chowdhury M, Wong J, Cheng A, Khilkin M, Palma E. Methadone Therapy in Underserved Urban Community: QTc Prolongation and Life-Threatening Ventricular Arrhythmias. Cardiovasc Ther. 2015 Jun;33(3):127-33.

Stringer J, Welsh C, Tommasello A. Methadone-associated Q-T interval prolongation and torsades de pointes. Am J Health Syst Pharm. 2009 May 1;66(9):825-33.

Pani PP, Trogu E, Maremmani I, Pacini M. QTc interval screening for cardiac risk in methadone treatment of opioid dependence. Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD008939.