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METHADONE

LAND ACKNOWLEDGEMENT

I respectfully acknowledge that I am a humble guest on the unceded homelands of the xʷməθkwəy̓əm (Musqueam), Sḵwx̱wú7mesh (Squamish), and Səl̓ílwətaɬ(Tsleil-Waututh) Nations.

OBJECTIVES

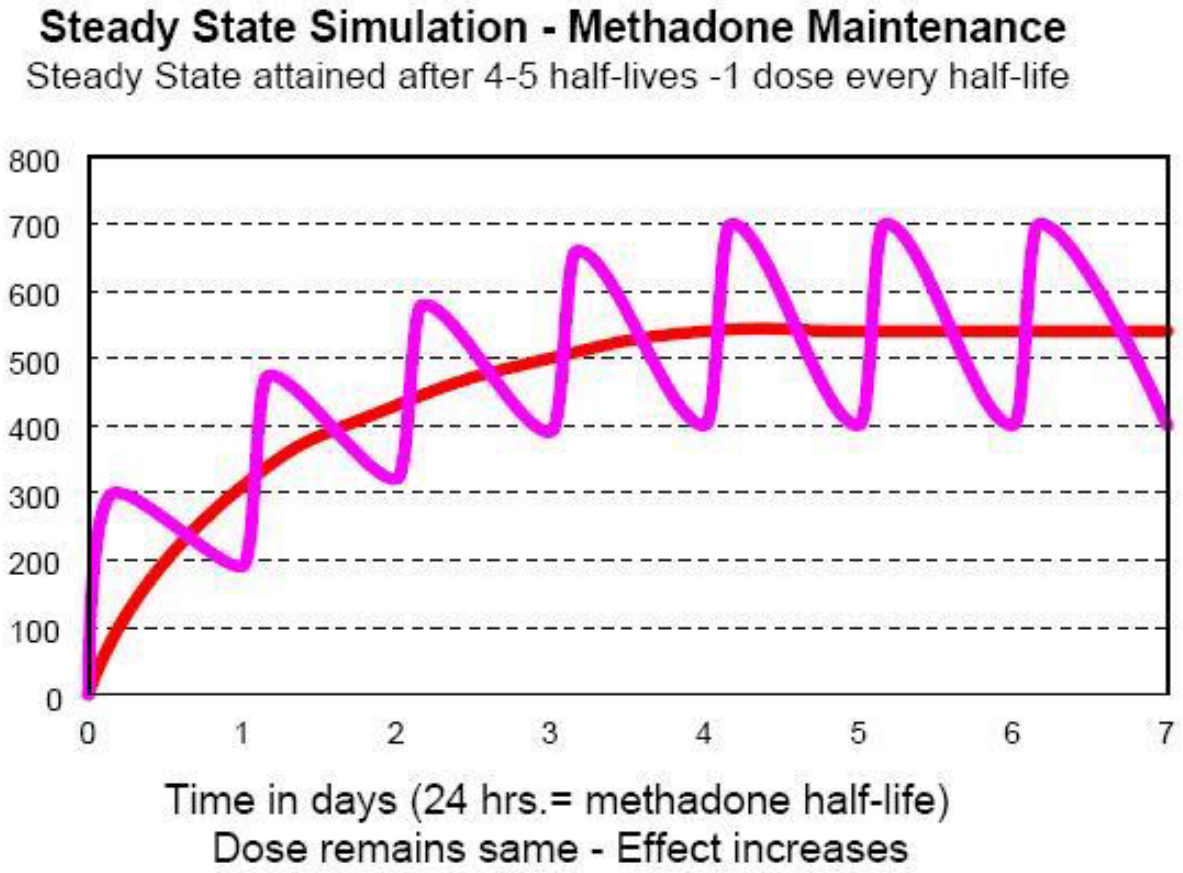
- Review Pharmacology
- QTc Prolongation
- Review relevant guidelines for NPs and RNs
- Initiation
- Maintenance
- Stabilization
- Missed Doses
- UDS
- Carries
- Benefits/Drawbacks
- Special Considerations

METHADONE

- Synthetic, long-acting full mu opioid agonist
- Active by IV, PO routes
- Indications:
  - Opioid Use Disorder
  - Pain
- Supplied:
  - 10mg/ml liquid (most common)
  - Tablets (generally for chronic pain only)

PHARMACOLOGY

- Dose peaks in 3hrs
- $T_{1/2}$ = 6-90 hours (24hrs)
- Steady state – 5 days



PHARMACOLOGY

- Metabolized primarily by the liver
  - CYP 450 isoforms (mainly 3A4) → many drug interactions

CYP 3A4 Inhibitor (↑ Methadone Concentration)	CYP 3A4 Inducers (↓ Methadone Concentration)
• Azole antifungals • Macrolide antibiotics • Protease inhibitor • Citalopram • Cannabidiol • Grapefruit juice	• Carbamazepine • Phenytonin • Rifampicin/rifampin • St. John's Wort • Topiramate

*Not an exhaustive list

PHARMACOLOGY

- Other Drug-Drug Interactions
  - Any other CNS depressants → additive effect
  - Other QTc prolonging medications → additive effect
  - Serotonergic medications → risk of serotonin syndrome

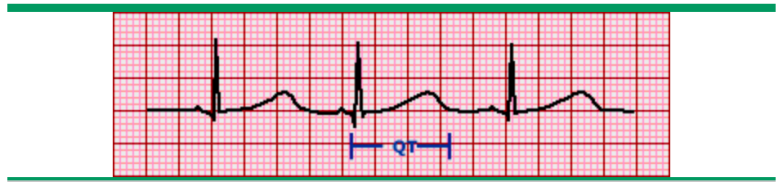
QTC PROLONGATION

- Associated with increased risk of polymorphic ventricular tachycardia (Torsades de Pointes)

- Normal QTc
  - Males <450 ms
  - Females <460 ms

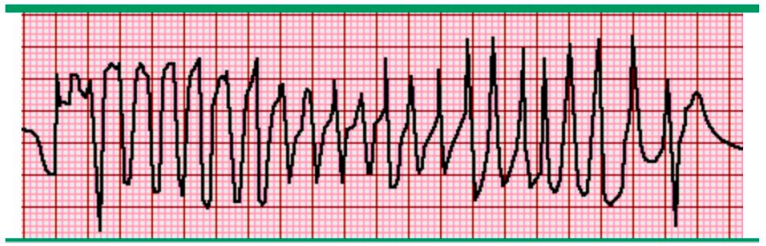
- Approach to management?

Single-lead electrocardiogram showing a prolonged QT interval



The corrected QT interval (QTc) is calculated by dividing the QT interval (0.60 seconds) by the square root of the preceding RR interval (0.92 seconds). In this case, the QTc is 0.625 seconds (625 milliseconds).

Single lead electrocardiogram (ECG) showing polymorphic ventricular tachycardia (VT)



This is an atypical, rapid, and bizarre form of ventricular tachycardia that is characterized by a continuously changing axis of polymorphic QRS morphologies.

ONTARIO STANDARDS

- NPs
  - Controlled Drugs and Substances education
- RNs can administer methadone
    - No additional training required

METHADONE INITIATION

- Establish active opioid use disorder diagnosis
- Confirm medication history
- Some clinics may require:
  - Patient-pharmacy-prescriber contract
  - UDS
  - Physical exam
  - Possible other diagnostic tests: HIV/HCV serology, LFTs, ECG, BhCG

METHADONE INITIATION

As per Ontario Guidelines

- Starting doses: 10mg-30mg PO OD
- When initiating, all doses are witnessed – no carries x 8 weeks

PHN: 123456789 Prescribing Date: Mar 1, 2021
First Name: John Last Name: Doe
Address: 123 Fake St, Toronto, ON. DOB: Jan 1, 2000

Drug Name and Strength: Methadone 10mg/ml

March 1, 2021-March 7, 2021, inclusive:
Methadone 10mg/ml: 30mg (thirty) PO OD DWI

Patty Wilson, NP

Patty Wilson

66160
Fake Clinic
Fake Address

METHADONE INITIATION

- Alternative Regimens (**off-label**)
  - **Consultation with Addiction Medicine Specialist Recommended**

<u>In-patient</u>

  - Methadone 30mg PO OD
    - Methadone 10mg q3h PRN. Max 3 doses in 24hrs. On day 4/5 – doses consolidated
    - Hold 10mg PRN dose if there is sedation

	Day 1	Day 2	Day 3	Day 4	Day 5
Scheduled	30mg	30mg	30mg	30mg	70mg
PRNs	10mg x 3	10mg x 3	10mg x 3	10mg x 3	D/C
Total	60mg	60mg	60mg	60mg	70mg

METHADONE INITIATION

- Alternative Regimens (**off-label**)
  - **Consultation with Addiction Medicine Specialist Recommended**

  <u>Community Patient and In-Patient</u>
  - Methadone 40mg PO OD starting dose
  - Addition of Hydromorphone IR tablets
    - Community Ex: Methadone 30mg PO OD DWI

      AND
    - HM IR 8mg tabs. 1-2 tabs q4h PRN. M: 10 tabs. Daily dispense – no witnessed ingestion.
      - Max 14 tabs/day

METHADONE INITIATION

- Health Teaching
  - Several weeks to stabilize
  - Avoid safety sensitive jobs until stable
  - Frequent visits when stabilizing
  - Avoid sedating medications, substances
  - Side effects
  - Steps to assist with fast titration

- Community Initiation Pearls
  - Verify pharmacy is appropriate
  - Good pharmacy relationships
  - Fax Rx into pharmacy

METHADONE STABILIZATION

- Doses 60mg-120mg are more effective than lower doses for retention
- As per Ontario Guidelines:
  - Weekly assessment during early stabilization
  - In-person assessment prior to dose adjustment

For Doses ≤ 80mg

Low Opioid Tolerance	Moderate Opioid Tolerance	High Opioid Tolerance
No more than 5mg dose increase every 5 days	5-10mg dose increased every 3-5 days	10-15mg dose increases every 3-5 days

- After 80mg – no more than 10mg increases q5-7 days

METHADONE STABILIZATION

- Alternative Regimens (**off-label**)
  - **Consultation with Addiction Medicine Specialist Recommended**

  <u>Community</u>
  - Phone call check-ins prior to dose adjustments
  - Check-ins with every 2-3 dose adjustments
  - Continue with 10mg dose increases q3 days past 80mg OD

METHADONE MAINTENANCE

As per Ontario Guidelines

- Defined as doses >80mg
- Assessed weekly to monthly
- ECG once dose >150mg, again at 180mg-200mg
  - ECG at 120mg for those with TdP risk factors

METHADONE MAINTENANCE

Alternative Regimens (**off-label**)

- **Consultation with Addiction Medicine Specialist Recommended**

  <u>Community</u>

  - Continue with 10mg dose increases q3 days past 80mg OD

METHADONE MISSED DOSES

1. Why do we taper missed doses?
2. What if a client vomits a dose?
3. What if a client is unable to come to the pharmacy to have their dose witnessed?

Table 08: Management of Missed Doses

Phase of Treatment	Missed Doses	Action	Dose Change
Early Stabilization (0-2) weeks	1 day missed	No dose increase	• Resume same dose. • Do not increase dose until 3 consecutive days at the same dose.
	2 consecutive days missed	• Reassess patient in person. • Cancel remainder of prescription	• Restart at initial dose (10-30 mg) for at least 3 days • Reassess after 3rd consecutive dose.
Late Stabilization/ Maintenance	1-2 days missed	• Provide usual prescribed dose if patient is not intoxicated. • Assess patient in 1-2 weeks to determine clinical stability	• No change
Late Stabilization/ Maintenance	3 consecutive days missed	• Reassess patient in person • Cancel remainder of prescription • Reassess every 3-4 days if dose is increased daily	• Restarted at 50% of regular dose or decrease to 30 mg • Then increase dose to no more than 10 mg daily for maximum of 3 days, then reassess by day 3-4. • There after, dose increase of 10-15 mg every 3 -5 days until 80 mg • Then 10 mg every 5-7 days for dose increases above 80 mg
Late Stabilization/ Maintenance	4 or more consecutive days missed	• Re-assess patient in person • Cancel remainder of prescription	• Restart at 30 mg or less • Then increase dose no more than 10-15 mg every 3-4 days until 80 mg • Then increase 10 mg every 5-7 days for dose increases above 80 mg.

METHADONE - UDS

- As per Ontario Guidelines UDS required:
  - At initiation
  - Ideally supervised or some other tamper mechanism in place
  - 4 or more times a month during stabilization phase or if working towards carries

"Frequent urines may be collected once to twice a week during the stabilization phase. Twice weekly urines will more likely detect sporadic drug use and in some patients might facilitate more accurate self disclosure. The MMT physician should ensure that frequent twice weekly urines do not interfere with the patient's work or family obligations." (pg48, CPSO MMT Guidelines)

METHADONE - UDS

Published in final edited form as:

Int J Drug Policy. 2019 February ; 64: 30–33. doi:10.1016/j.drugpo.2018.08.006.

Lacking evidence for the association between frequent urine drug screening and health outcomes of persons on opioid agonist therapy

Jasmine McEachern[1], **Lauren Adye-White**[1], **Kelsey C. Priest, MPH**[2,3], **Eloise Moss**[4], **Lauren Gorfinkel**[1], **Evan Wood**[1,4], **Walter Cullen**[5], and **Jan Klimas**[1,4,5]

Results: Of the 60 potentially eligible articles reviewed, only one three-arm randomized open-label trial, comparing weekly and monthly UDS testing with take-home OAT doses, met our inclusion criteria.

This three-arm randomized open-label trial (N = 53) compared treatment outcomes for participants receiving take-home doses of methadone. All participants in the included study were patients enrolled in a methadone outpatient clinic – 60% were male; mean age of 38 years. The duration of the trial was 28 weeks. Participants assigned to the intervention groups received take-home doses contingent on random weekly or monthly negative UDS tests for opiates or cocaine. The control group received take-home doses randomly, independently of the testing result. Based on a "time-course analysis" this study found that take-home doses, contingent on drug-free urines, prevent a decline in treatment performance and retention over time, sustained with testing as infrequently as once per month. After assessing Chutuape et al. with the Cochrane risk of bias assessment tool (Higgins & Green, 2011), the study was determined to be of a high risk of bias due to a lack blinding of treatments, an unclear allocation concealment and blinding of outcomes (see details of quality rating and study characteristics in Table 1).

METHADONE - UDS

- 2 different types – POC, Immunoassay
- Methadone
  - Look for methadone *and* EDDP

REVIEW

MAYO CLINIC

CrossMark Clinical Interpretation of Urine Drug Tests: What Clinicians Need to Know About Urine Drug Screens

Karen E. Moeller, PharmD, BCPP; Julie C. Kissack, PharmD, BCPP; Rabia S. Atayee, PharmD, BCPS; and Kelly C. Lee, PharmD, MAS, BCPP

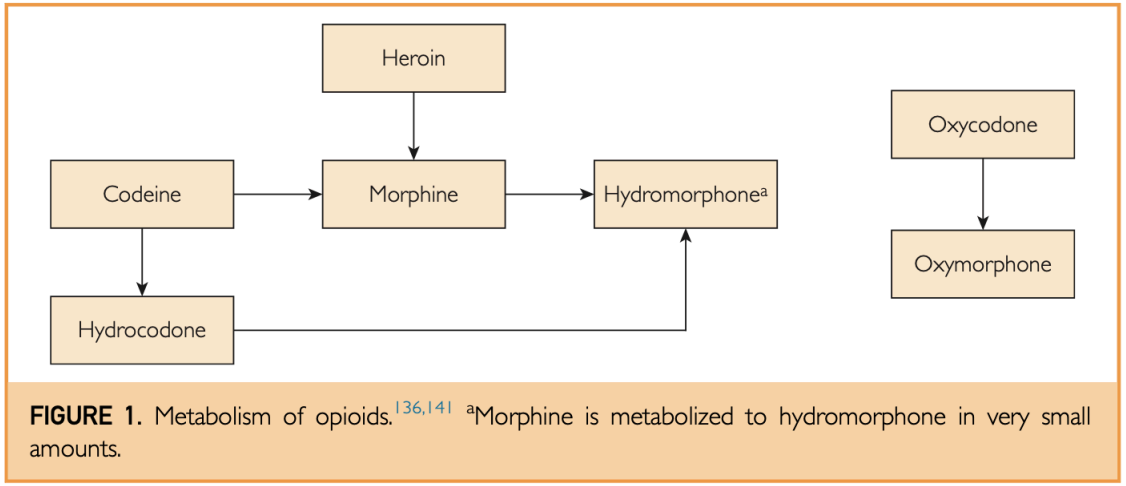


FIGURE 1. Metabolism of opioids.[136,141] [a]Morphine is metabolized to hydromorphone in very small amounts.

Mayo Clin Proc. ■ May 2017;92(5):774-796 ■ http://dx.doi.org/10.1016/j.mayocp.2016.12.007
www.mayoclinicproceedings.org

METHADONE CARRIES

Ontario Guidelines

- Requirements:
  - Safe storage →Housed, portable lockbox
  - UDS – shows only methadone and EDDP in the week prior
  - Stable dose
- Schedule:
  - First carry at 8 weeks
  - Each subsequent carry no faster than q4weeks
  - Max 6 take-home doses/week (13 in special circumstances)

METHADONE BENEFITS

- Better treatment retention than buprenorphine/naloxone
- No maximum dose
- Easy initiation
- Therapeutic doses associated with adherence to ARVs, reduction in injection drug use

METHADONE DRAWBACKS

- Highest risk of overdose compared to other OAT
  - Recent study reported that methadone was involved in 7.4% of opioid deaths in BC[1]
- Requires DWI
- Side Effects
- Weeks to achieve therapeutic dose
- Many drug-drug interactions

1. Crabtree A, Lostchuck E, Chong M, Shapiro A, Slaunwhite A. Toxicology and prescribed medication histories among people experiencing fatal illicit drug overdose in British Columbia, Canada. CMAJ. 2020; 24(192): E967-E972 doi: 10.1503/cmaj.200191

METHADONE – SPECIAL CONSIDERATIONS

Unless a Regular Part of your Practice – Addiction Medicine Specialist Consult Recommended

- Acute pain
- Pregnancy
- Primary care needs
- Bundling care
- Concurrent AUD
- Concurrent BZD Rx or use disorder
- Tapering off

QUESTIONS?