Clinical Management of Opioid Use Disorder- Methadone

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Faculty/Presenter Disclosure

- **Faculty:** Aida Sadr
- **Relationships with financial sponsors:** None

Overview

In the next 30 minutes, I will *briefly* review:

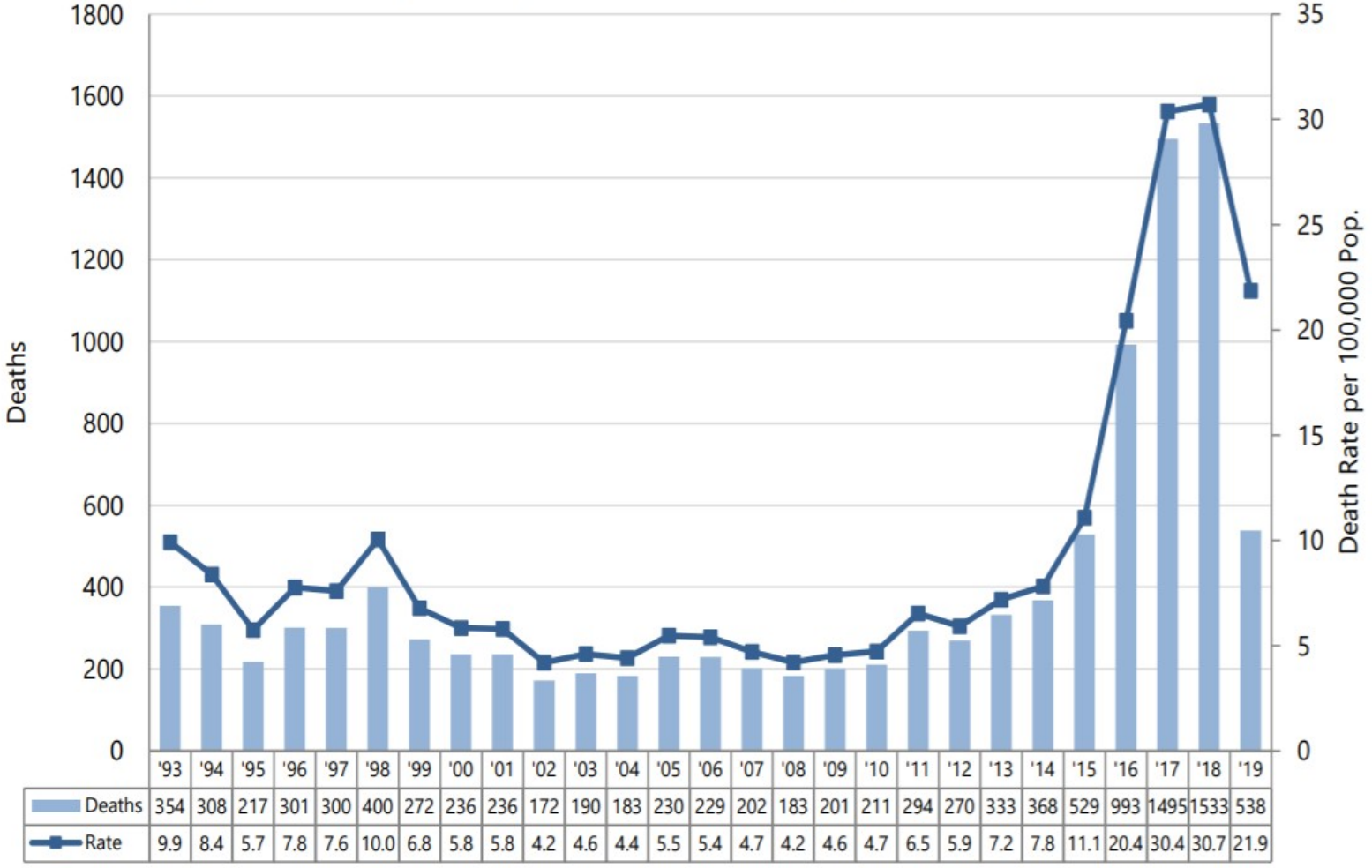
- Current state of the Drug Poisoning Epidemic in BC
- Approach to the Clinical Management of Opioid Use Disorder
- Methadone Pharmacokinetics, Initiation, Titration

But spend more time on what has challenged me in my practice and/or recent changes I've made to my practice:

- New formulation of Methadone Hydrochloride (Metadol-D®)
- Restarting Dose Considerations
- Dose Titrations
- QTc monitoring
- OUD/OAT and Driving

Illicit Drug Toxicity Deaths in BC

Figure 1: Illicit Drug Toxicity Deaths and Death Rate per 100,000 Population [3-6]



	'93	'94	'95	'96	'97	'98	'99	'00	'01	'02	'03	'04	'05	'06	'07	'08	'09	'10	'11	'12	'13	'14	'15	'16	'17	'18	'19
Deaths	354	308	217	301	300	400	272	236	236	172	190	183	230	229	202	183	201	211	294	270	333	368	529	993	1495	1533	538
Rate	9.9	8.4	5.7	7.8	7.6	10.0	6.8	5.8	5.8	4.2	4.6	4.4	5.5	5.4	4.7	4.2	4.6	4.7	6.5	5.9	7.2	7.8	11.1	20.4	30.4	30.7	21.9

https://www2.gov.bc.ca/assets/gov/birth-adoption-death-marriage-and-divorce/deaths/coroners-service/statistical/illicit-drug.pdf

Drug Supply Poisoning

Figure 1: Percent of Illicit Drug Deaths with Fentanyl Detected

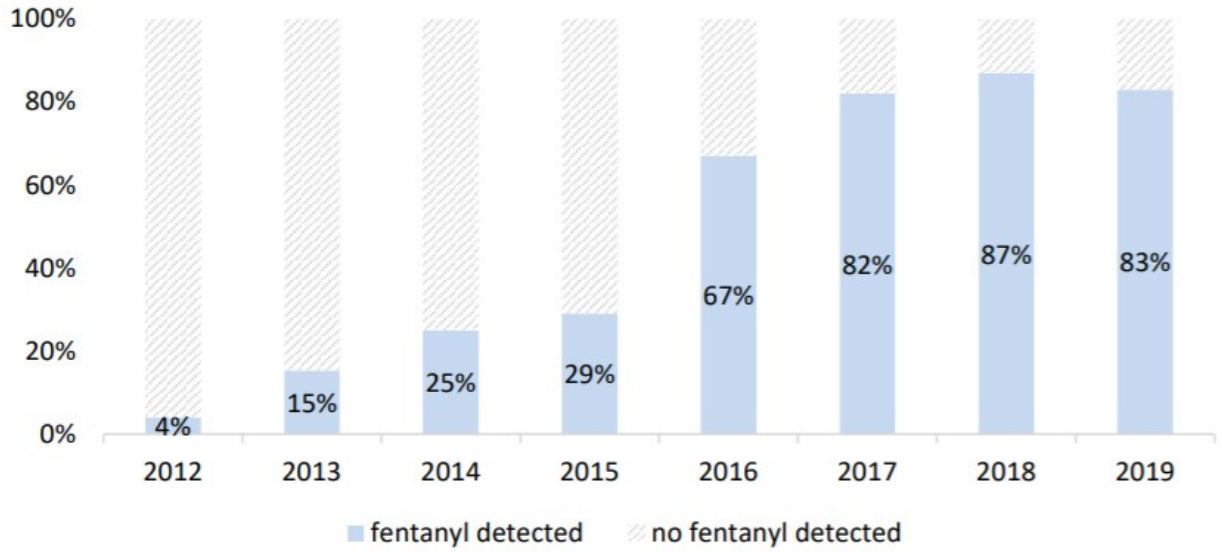
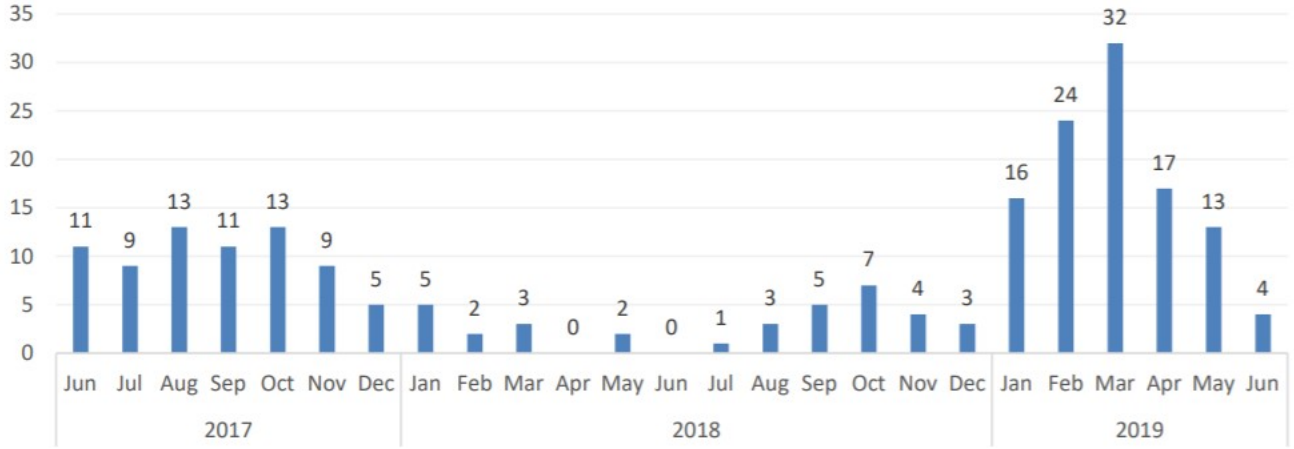


Figure 2: Illict Drug Overdose Deaths with Carfentanil Detected



https://www2.gov.bc.ca/assets/gov/birth-adoption-death-marriage-and-divorce/deaths/coroners-service/statistical/fentanyl-detected-overdose.pdf

OPIOID USE DISORDER (OUD)- DSM V

- The diagnosis of Opioid Use Disorder under DSM V can be applied to someone who uses opioid drugs and has at least **two of the following symptoms within a 12 months period**:
  - Taking more opioid drugs than intended.
  - Wanting or trying to control opioid drug use without success.
  - Spending a lot of time obtaining, taking, or recovering from the effects of opioid drugs
  - Craving opioids
  - Failing to carry out important roles at home, work or school because of opioid drugs.
  - Continuing to use opioids, despite use of the drug causing relationship or social problems.
  - Giving up or reducing other activities because of opioid use.
  - Using opioids even when it is physically unsafe.
  - Knowing that opioid use is causing a physical or psychological problem, but continuing to take the drug anyway.
  - Tolerance for opioids.
  - Withdrawal symptoms when opioids are not taken.
- Mild: two to three Moderate: four to five Severe: Greater than five

Clinical Management of OUD

Table 1. Clinical management of opioid use disorder

WITHDRAWAL MANAGEMENT [1–3]

Tapered methadone, buprenorphine, or alpha$_2$-adrenergic agonists

+/– psychosocial treatment [4]
+/– residential treatment
+/– oral naltrexone [5]

AGONIST THERAPIES

Buprenorphine/naloxone [6] *(preferred)*

Methadone [7,8]

+/– psychosocial treatment
+/– residential treatment

SPECIALIST-LED ALTERNATIVE APPROACHES

Slow-release oral morphine [9,10]

+/– psychosocial treatment
+/– residential treatment

TREATMENT INTENSITY

LOW
If opioid use continues, consider treatment intensification. »

HIGH
Where possible, « simplify treatment.

HARM REDUCTION [11-13]

Across the treatment intensity spectrum, evidence-based harm reduction should be offered to all, including:

- Education re: safer user of sterile syringes/needles and other applicable substance use equipment
- Access to sterile syringes, needles, and other supplies
- Take-Home-Naloxone (THN) kits
- Access to Supervised Injection Sites (SIS)

http://www.bccsu.ca/wp-content/uploads/2017/06/BC-OUD-Guidelines_June2017.pdf

Withdrawal Management/Detox

BRITISH COLUMBIA CENTRE ON SUBSTANCE USE
Networking researchers, educators & care providers

Safety Bulletin

August 29, 2017

Avoid the use of withdrawal management as a standalone treatment for opioid use disorder

Recommendation

Withdrawal management alone is not an effective treatment for opioid use disorder, and offering this as a standalone option to patients is neither sufficient nor appropriate. Care providers should clearly communicate to patients the risks of withdrawal management as a standalone strategy and encourage a period of opioid agonist therapy or a slower outpatient taper (e.g., > 3 months) with methadone or buprenorphine/naloxone.

In the event that patients choose to proceed with withdrawal management without follow-up treatment, providers may consider using an informed consent form or waiver to document that this decision has been made against medical advice. A sample waiver is appended to this document.

Risks of Detox

Acute withdrawal management (also known as "detox") is an intervention aimed at reducing health harms, such as withdrawal seizures, associated with substance use cessation. However, as a standalone intervention, withdrawal management does not constitute "addiction treatment," and can be associated with harm, especially in the context of opioid use disorder.

What the Research Says

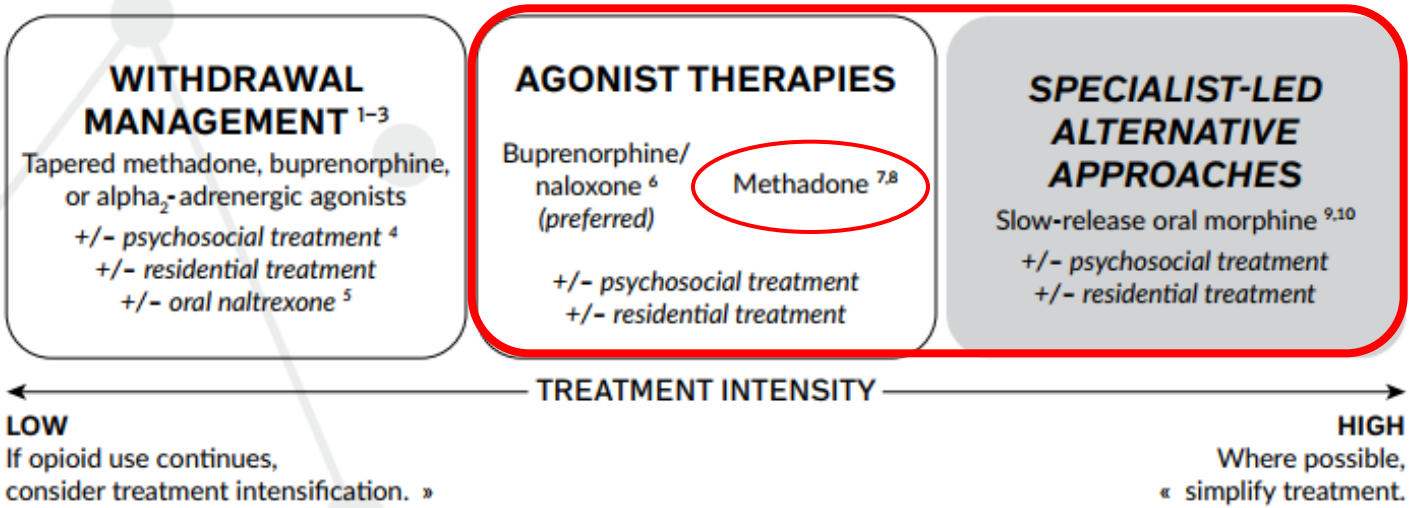
Research has shown that, when offered as an isolated intervention for opioid use disorder, inpatient withdrawal management may leave patients particularly vulnerable to the following serious health harms:

- Nearly universal rates of relapse to opioid use – Abrupt (e.g., < 1 week) taper off of opioids results in the vast majority of individuals returning to opioid use.[1]
- Elevated risk of overdose – Individuals who relapse following withdrawal management are at increased risk of overdose as a result of the rapid loss of tolerance to opioids.[2]
- Elevated risk of infection – Studies have shown that, in comparison to offering nothing, persons who inject drugs who undergo withdrawal management are more likely to contract HIV and Hepatitis C, likely as a result of high risk behaviours upon relapse.[3,4]

Au http://www.bccsu.ca/wp-content/uploads/2017/08/Safety-Bulletin-Withdrawal-Management.pdf

Clinical Management of OUD

Table 1. Clinical management of opioid use disorder



HARM REDUCTION [11-13]

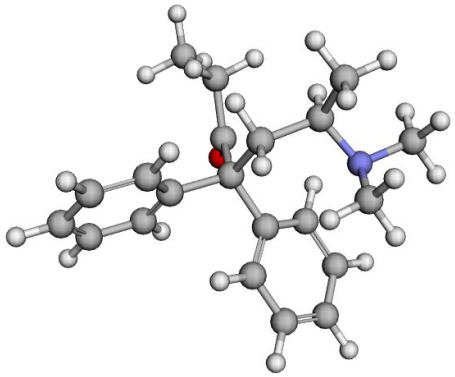
Across the treatment intensity spectrum, evidence-based harm reduction should be offered to all, including:

- Education re: safer user of sterile syringes/needles and other applicable substance use equipment
- Access to sterile syringes, needles, and other supplies
- Take-Home-Naloxone (THN) kits
- Access to Supervised Injection Sites (SIS)

OAT Rx Considerations:

- **Effectiveness:**
  - Personal Stability (Cravings/WD)
  - Cessation of Illicit Opiate Use (-ve UDS)
  - Social Stability (Employment / Crime / Housing / Connection to Family & Friends)
  - Retention in care
  - Survival
- **Patient Factors/ Preference**
- **Provider Factors / Preference**
- **Adverse Events / Safety**
- **Drug Interactions**
- **Induction Time & Dose Administration**
- **Misuse / Diversion Risk**

Methadone



- Long-acting synthetic opioid agonist
- Binds to and occupies mu-opioid receptors (full agonist activity) and prevents withdrawal for 24+ hrs, reduces cravings, and reduces euphoric effects of illicit opioid use
- **Good oral bioavailability:** 80-95%; rapid absorption post oral administration and detectable serum levels 30 min post dose
- **Duration:** time to peak plasma concn/clinical effect 4 hrs (range of 2-6h)
  - Plasma half-life ~24-36h at steady state; d/t long half life, can accumulate
  - Takes 4-5 day for methadone plasma levels to reach steady state q dose change
- **Tolerance:** is lost in as little as 3 days
- **Dosing**: higher doses (60-120mg/day+) more effective than lower doses for treatment retention and reducing illicit opiate use *
  - *high degree of inter-individual variability in pharmacokinetics/metabolism so individualized approach needed

Methadone- Adverse Effects

- Constipation
- Drowsiness
- Excess sweating
- Opiate Induced Hypogonadism
- QTc prolongation → torsades de pointes
- Risk of overdose*
  - As a full agonist, greater potential for lethal OD compared w/ buprenorphine
  - Risk higher w/ concurrent benzodiazepine and/or ETOH use
  - *MMT associated w/ reduced overall mortality rates w/ a 70% reduction in risk of mortality (esp d/t heroin OD) among pts on MMT cf untreated OUD[1]
- Drug-Drug Interactions
  - Methadone metabolized via cytochrome P450 enzyme system so many DDIs
  - Caution with other QTc prolonging meds
  - **MAKE USE OF ONLINE DDI CHECKERS**

1. Bell J, Zador D. A risk-benefit analysis of methadone maintenance treatment. Drug Saf 2000; 22:179.

Table 1: Drug Interactions with Methadone

Drugs that may increase methadone level	
• Amiodarone	• Fluvoxamine
• Cimetidine	• Grapefruit juice
• Ciprofloxacin	• Itraconazole
• Clarithromycin	• Ketoconazole
• Diazepam	• Nefazodone
• Echinacea	• Paroxetine
• Erythromycin	• Sertraline
• Ethanol (acute ingestion)	• Voriconazole
• Fluconazole	• Urinary alkalizers
	• Other P450 inhibitors
Drugs that may decrease methadone levels	
• Abacavir	• Phenobarbital
• Amprenavir	• Phenytoin
• Carbamazepine	• Primidone
• Cocaine	• Rifampin
• Efavirenz	• Risperidone
• Ethanol (chronic ingestion)	• Ritonavir
• Fosamprenavir	• Saquinavir
• Lopinavir/ritonavir	• St. John's wort
• Nelfinavir	• Urinary acidifiers
• Nevirapine	• Other P450 inducers

BC Pharmacare Coverage

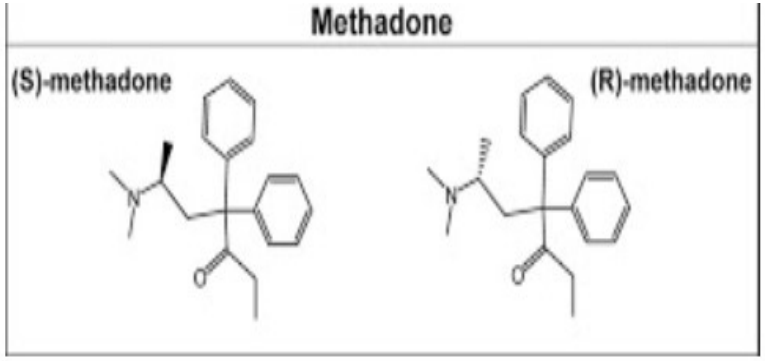
- Something I seldom thought about before I worked at Connections, where we see many patients who don't have OAT access purely due to coverage issues- so ask!

- As of June 5, 2017, Methadone, buprenorphine/naloxone, and SROM are fully covered under BC Pharmacare's Psychiatric Medication Plan (Plan G)- adjusted net income < 42K/yr

- Full coverage for above OAT available to those:
  - receiving BC Income Assistance (Plan C)
  - who do not have a deductible or family maximum under Fair PharmaCare
  - Registered in what used to be the Non-insured Health Benefit (NIHB) Plan, now transitioned to BC Pharmacare's Plan W

New formulation of methadone- Metadol-D®

- In 2014, BC changed the formulation of Pharmacare covered methadone from a 1mg/ml pharmacy compounded formulation to Methadose™, a 10mg/ml cherry-flavoured solution
- Many reports of patients previously stable on 1mg/mL formulation experiencing withdrawal symptoms and re-initiation of illicit drug use[1]
- Methadone is a racemic mixture and different formulations may have different ratios of enantiomers and differing therapeutic benefits - needs more research[2]



1. Greer et al. Patient perspectives of methadone formulation change in British Columbia, Canada: outcomes of a provincial survey. Subst Abuse Treat Prev Policy. 2016; 11:3
2. https://www.bcpharmacy.ca/news/methadosetm-or-metadol-dr

New formulation of methadone- Metadol-D®

- Metadol-D® is clear, colourless, unflavoured 10mg/ml solution that must be diluted to 100ml in Tang or Crystal Light
- Initially required SA but as of May 28, 2019, Metadol-D is now available and 100% covered
- As per latest BCCSU OAT Update:

Transitioning your patient from Methadose™ to Metadol-D®:

1. Discuss potential risks and benefits of the transition with your patient.
2. If a shared decision is made to switch methadone products, document the discussion, decision, and your clinical rationale carefully in the patient's medical record.
3. Write a new prescription for **Metadol-D®** (on the same prescription to allow for dispensing of whatever is available at the time) using the standard ***BC Methadone Maintenance Treatment Controlled Prescription Program Form***. (See example prescription on p. 3).
4. Call the patient's pharmacy and discuss the switch to ensure the product is available in adequate quantities.

Induction & Dosing Guidelines

As per BCCSU Guidelines (June 2017):

- **Initial dose should not exceed 30mg/day**; consider lower doses in those who have no tolerance/opioid-naïve or unknown tolerance (e.g. use ETOH, benzos)
- Doses should be slowly titrated upward by **5-10mg** at a time
- Doses can be increased at a rate of **5-10mg every 5 or more days**; more rapid dose titration should only be attempted under close supervision of experienced provider and/or specialized care centres that permit enhanced monitoring
- Missed Dose Protocol:

Missed Days (consecutive)	Dose	Suggested Dose Adjustment
1–2	Any dose	Same dose (no change)
3–4	30 mg	Same dose (no change)
	31–60 mg	Restart at 30 mg (lower dose if safety concerns)
	> 60 mg	Restart at 50% of previous dose
5 or more	Any dose	Restart at 5–30 mg (depending on tolerance)

BUT…

- The BCCSU Guidelines are currently in the process of being updated
- Local methadone prescribing practices have evolved in the last two years

CASE: Mr. M

- 45 yo male; Currently NFA and sleeping in Stanley Park
- Says he's HCV+ but nil else on CC; currently not on any other meds
- On and off OAT for years, mostly with methadone (tried Suboxone for a short stint but hated it)
- Pharmanet shows that he was last on methadone 4 months ago and got up to a dose of 110mg before he missed 3 days in a row, script was cancelled and he never made it back to the clinic….until today
- Currently using 1-2 g IV 'down' per day; He is alert, oriented, and wants to restart MMT

WHAT STARTING DOSE WOULD YOU OFFER HIM?

CASE: Mr. M

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- Currently using 1-2 g IV 'down' per day; He is alert, oriented, and wants to restart MMT
- **WHAT STARTING DOSE WOULD YOU OFFER HIM?**

FOR ANYONE RESTARTING METHADONE AND CLINICALLY ASSESSED TO HAVE HIGH OPIOID TOLERANCE AND WITH DOCUMENTED TOLERANCE (≥ 5 DAYS AT ≥ 40MG IN LAST YEAR), MAY RESTART AT A MAXIMUM OF 40MG

CASE: Mr. M

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- Pharmanet shows that he was last on methadone 4 months ago and got up to a dose of 110mg before he missed 3 days in a row, script was cancelled and he never made it back to the clinic….until today
- Currently using 1-2 g IV ‘down’ per day; He is alert, oriented, and wants to restart MMT
- **You choose to start him at 40mg, CLEARLY DOCUMENTING YOUR RATIONALE IN THE CHART**

WHEN SHOULD HE COME BACK FOR A DOSE INCREASE?

- **CONSIDER A DOSE INCREASE (MAX 10MG) ON DAY 3 OR 4 OF SAME CONSECUTIVE DOSE IF:**
  - **ABLE TO ASSESS PATIENT 2-4 HOURS POST DOSE AND**
  - **PATIENT AT HIGH RISK FOR ILLICIT DRUG OVERDOSE AND**
  - **THERE ARE NO CONTRAINDICATIONS TO A MORE RAPID DOSE ESCALATION**
- **EXAMPLE:**

  Day 1 (MMT start)- 40mg DWI

  Day 2- 40mg DWI

  Day 3- 40mg DWI at 8:30am, patient assessed at 10:30am and is alert, oriented, no CIs → 10mg top up dose (and new Rx written for 50mg DWI starting following day)

  Day 4- 50mg DWI
- Much easier to execute at places like DTC, RAAC; I find this difficult to do at VNH, for example

CASE: Mr. M

- Mr. M continues to follow-up at the clinic and gets up to a dose of 120mg
- Then it's Cheque Week and he loses track of time…. missing his dose on Wednesday, Thursday, Friday, Saturday
- Shows up to his pharmacy on Sunday and is informed his Script is cancelled so he returns to see you in clinic
- Following the BCCSU Guidelines, you appropriately dose reduce him by 50% to 60mg methadone DWI due to the 4 missed doses

WHEN CAN HE COME BACK FOR A DOSE INCREASE?

CASE: Mr. M

- Mr. M continues to follow-up at the clinic and gets up to a dose of 120mg
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WHEN CAN HE COME BACK FOR A DOSE INCREASE?

CONSIDER OFFERING A 'RAPID RETITRATION' (at a maximum rate of 10mg/day after two consecutive dose) WITH DAILY CLINICAL REASSESSMENT UNTIL PREVIOUS STABILIZATION DOSE HAS BEEN RE-ESTABLISHED*

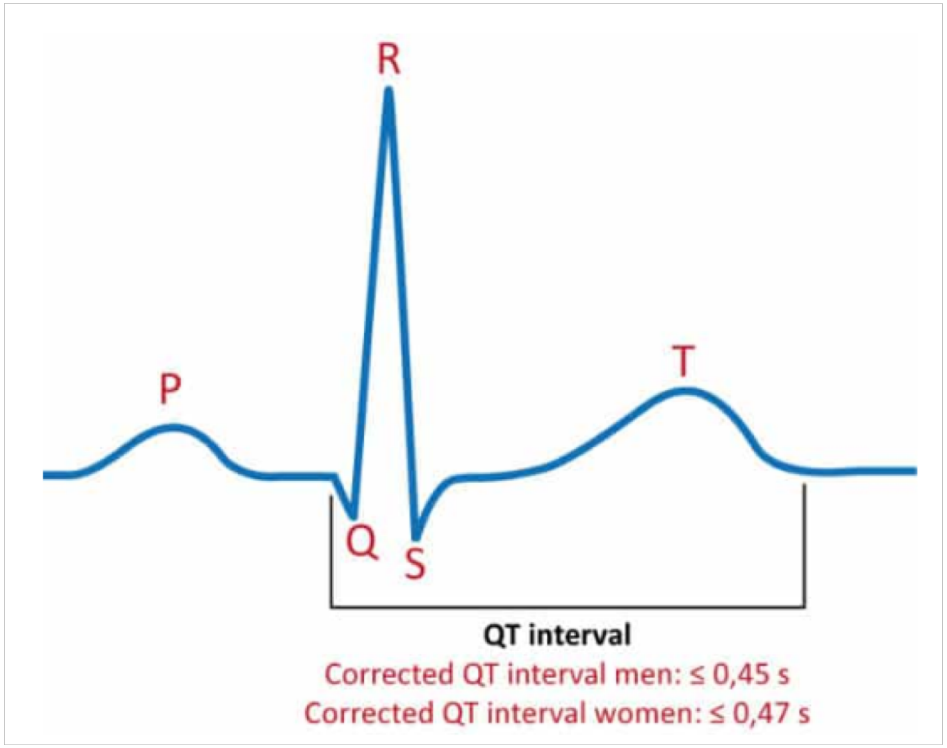
CASE: Mr. M

- In our patient's case, this would look like:
  - Sunday, restart at 60mg (50% dose reduction due to 4 missed doses)
  - Monday, 60mg DWI at 10am, reassessed at 12pm- alert, oriented, appropriate- top up dose of 10mg and new Rx
  - Tuesday, 70mg DWI
  - Wednesday, 70mg DWI; doesn't have time to wait around 2 hours
  - Thursday, pt assessed prior to getting his dose, new Rx written for 80mg DWI
- **5 or more missed doses will require a re-start (maximum 40mg) and then usual titration process**

REVIEW

- FOR ANYONE RESTARTING METHADONE AND CLINICALLY ASSESSED TO HAVE HIGH OPIOID TOLERANCE AND WITH DOCUMENTED TOLERANCE (≥ 5 DAYS AT ≥ 40MG IN LAST YEAR), CONSIDER RESTARTING AT A MAXIMUM OF 40MG
- CONSIDER A DOSE INCREASE (MAX 10MG) ON DAY 3 OR 4 OF SAME CONSECUTIVE DOSE IF:
  - ABLE TO ASSESS PATIENT 2-4 HOURS POST DOSE AND
  - PATIENT AT HIGH RISK FOR ILLICIT DRUG OVERDOSE AND
  - THERE ARE NO CONTRAINDICATIONS TO A MORE RAPID DOSE ESCALATION
- CONSIDER OFFERING A 'RAPID RETITRATION' WHEN DOSE REDUCING A PATIENT DUE TO MISSED DOSES (at a maximum rate of 10mg/day after two consecutive dose) WITH DAILY CLINICAL REASSESSMENT UNTIL PREVIOUS STABILIZATION DOSE HAS BEEN RE-ESTABLISHED

AND NOW FOR EVERYONE'S FAVOURITE TOPIC:



QTc- should we screen?

- Methadone use has been associated with QTc prolongation & TdP
- Many of those who develop TdP have other RFs for this arrythmia
- BCCSU Guidelines currently do not have a specific recommendation re QTc screening
- "Methadone and QTc screening: Weighing the risks and benefits" by Drs. Seonaid Nolan & Evan Wood:
  - "until further research can validate the utility of routine ECG screening, we recommend against its use unless clinicians feel that a change in the methadone regimen would pose a lower risk than the theoretical risk of a potentially prolonged QTc"
  - "While existing data should be viewed with some skepticism given the inability to accurately ascertain causes of death in this population, **the mortality of methadone induced TdP has been estimated at 0.06 deaths per 100 patient years whereas that associated with untreated heroin dependence is approximately 1 to 3 deaths per 100 person years**

Ok, sooo, don't screen?

Nolan, S & Wood, E. (2014). Methadone and QTc screening: Weighing the risks and benefits. CJAM Canadian Journal of Addiction Medicine. 5. 17-19.

DTES Connections: Prolonged QTc Protocol

- Continue to recommend ECG screening for prolonged QTc @ ~ 150mg of methadone or higher, and earlier if known risk factors for Torsades de Pointes
  - Continue to offer ongoing OAT titration as per usual goals & methods if documented, informed consent of the theoretical risks of unrecognized Long QTc ;
  - continue to recommend ECG screening and
  - offer support of CLW/Peer team to support in getting to Lifelabs
  - stop dose increases at 200mg methadone; until ECG is completed

- If ECG completed, and QTc > 470ms for men or >480ms for women:
  - Discuss risks of arrhythmia vs. individual benefits of ongoing OAT
  - Consider the following options:
    - Review other QTc prolonging medications that might be adjusted/discontinued
    - Repeating ECG
    - Switching to Kadian or Suboxone
    - Continuing Methadone; w/ documented informed consent
    - Consider repeating periodically for monitoring

- If ECG completed, and QTc > 500ms:
    - Review other QTc prolonging medications that might be adjusted/discontinued & repeat ECG
    - And/or recommend switching to Kadian or Suboxone

*Risk Factors include (but not limited to):

- Multiple QT prolonging medications
- Bradycardia
- Electrolyte disturbances (especially hypokalemia, hypomagnesemia)
- Structural Heart Disease (CHF, MI, LVH)
- Female Sex
- Advanced Age
- Congenital Long QT / ? family history of sudden cardiac death

OUD, OAT & DRIVING

- More relevant in some practices than others
- Hot topic with little published guidance on the issue (just ask Dan!)
- After many debates, our current clinic guideline is the following:
  - All patients are screened for driving at intake and reminded to never drive nor operate machinery while intoxicated or sedated from ANY substance
  - Due to the increased risk of sedation, recommended that all patients starting on an opioid (including OAT) do not drive until dose is at a steady-state* and there's no evidence of sedation/impairment
  - If anyone is known to continue driving when intoxicated/sedated and/or during the OAT dose titration phase, following the direction to voluntarily abstain from driving**, physicians have a legal duty to report to Road Safe BC** (who then make a decision about whether to revoke a driver's license)
- Hopefully, the new BCCSU Guidelines will provide further guidance on this topic…

OAT Rx Considerations:

OAT Rx	Effectiveness	Patient Factors / Preference	Provider Factors	Adverse Events /Safety	Drug Interactions	Induction Time / Dose Administration	Misuse / Diversion Risk
Methadone	Highly effective	• Familiar • Pain	• Familiar • no office induction	• QTc ^ • Risk of OD	• multiple common DDIs • Benzos, ETOH	• Easy to initiate • Slower to reach steady state	Low with DWI
Suboxone							
SROM							

Questions? Comments?

Thank you!