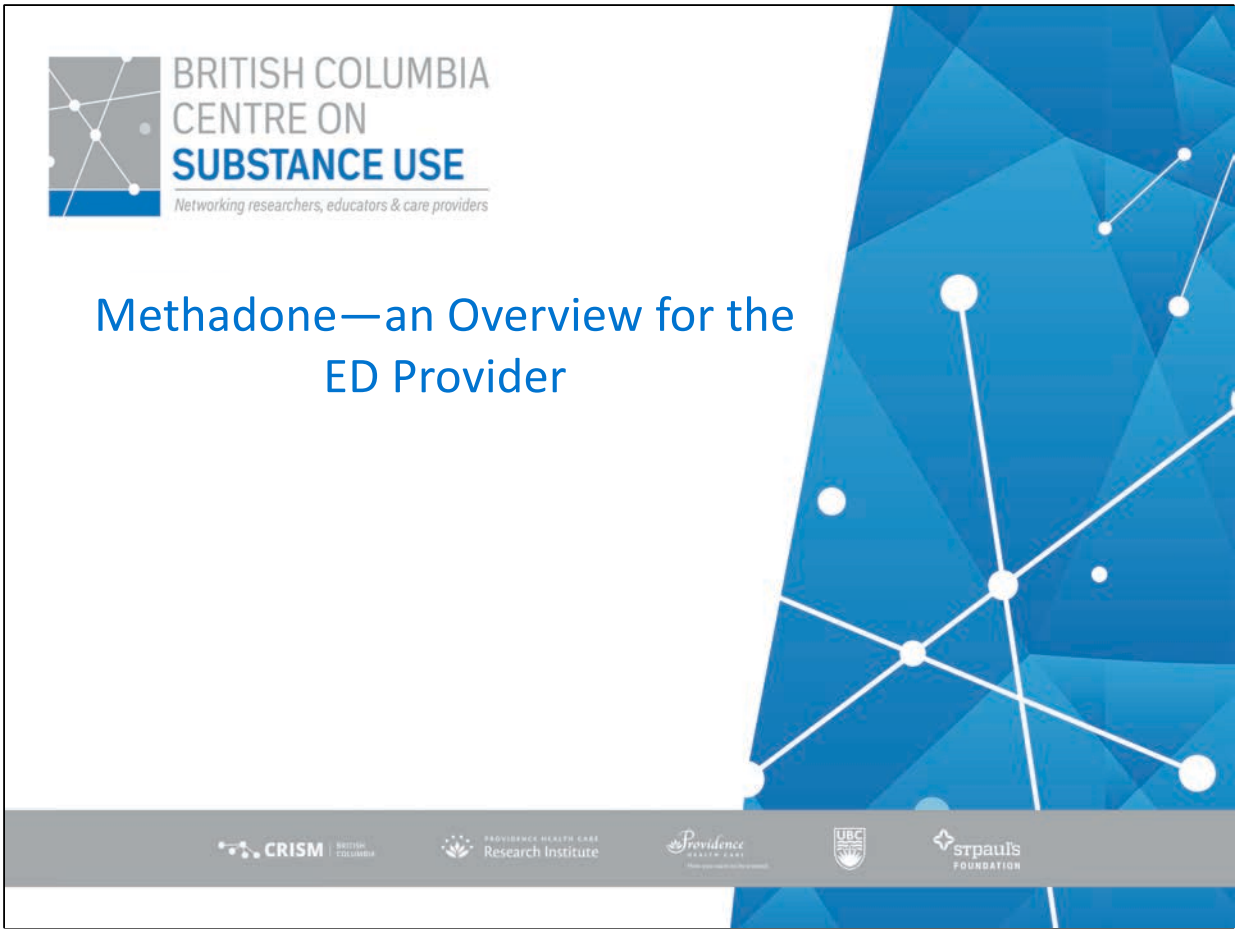
BRITISH COLUMBIA
CENTRE ON
SUBSTANCE USE
Networking researchers, educators & care providers
Methadone—an Overview for the
ED Provider
CRISM
Research Institute
Providence
UBC
St Paul's
FOUNDATION

We respectfully acknowledge the land on which we work is the unceded traditional territory of the Coast Salish Peoples, including the traditional territories of xʷməθkwəy̓əm (Musqueam), Sḵwx̱wú7mesh (Squamish), and səl̓ílwətaɬ (Tsleil-Waututh) Nations

Learning Objectives

1. Methadone—the basics
   - Review of the evidence
   - Pharmacologic properties
   - Disadvantages
   - Prescribing: initiation, titration and missed doses
2. Emergency department presentations
   - Missed doses
   - Initiation
   - Toxicity
   - Tolerance
   - Withdrawal
   - Prolonged QTc

1. Methadone—the Basics

Methadone—A Strong Evidence Base

- Methadone has been shown to:
  - ↓ All cause mortality
  - ↓ Risk of HIV/HCV
  - ↑ Retention to treatment
  - ↑ Rates of abstinence
- It is considered second line medication for OUD due to increased risk of toxicity and adverse event relative to buprenorphine

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1. Larochelle MR, Bernson D, Land T, Stopka TJ, Wang N, Xuan Z, et al. Medication for Opioid Use Disorder After Nonfatal Opioid Overdose and Association With Mortality. Ann Intern Med [Internet]. 2018 Jun 19;169(3):137–18. Available from: http://annals.org/article.aspx?doi=10.7326/M17-3107
2. British Columbia Centre on Substance Use and B.C. Ministry of Health. A Guideline for the Clinical Management of Opioid Use Disorder. Published June 5, 2017.

Pharmacologic Properties of Methadone

- Mu receptor: full agonist
- Peak: 3 hours (2-4 hours)
- Duration: 24–96 hours at steady state
- Steady state: average 5 days
- Metabolism: hepatic

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- Variability in metabolism can lead to variation in duration to reach steady state. Some patients may require up to 7 days or more.
- This pharmacologic principle is important to recognize, as the dose of methadone won't have a full effect until after 5 doses in a row are administered—hence why increases may only occur after 5-7 days

Drug–Drug Interactions

- Consider methadone to be the ”warfarin of addiction” due to the many medications that can
  - Alter blood levels through interaction with CYP3A4 enzyme
  - Enhance its sedative effects.
- Common medications include ARVs, certain antibiotics (rifampin), anticonvulsants and benzodiazepines.

Side effects and Disadvantages of Methadone

- Methadone is linked to increased rates of overdose and sedation in combination with sedatives (and other sedating medications)
- Its variable metabolism makes it difficult to predict toxicity
- Methadone can prolong QTc
  - ↑ Risk with doses >100mg
- Long term side effects include:
  - Lower bone mineral density

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Lower bone mineral density (Grey et al 2006, Milos et al 2011)

Prescribing Methadone

Initiation	30mg (5–40mg)
Titration	↑ q5days: 5–10mg * Slower if higher risk of opioid toxicity
Stabilization	80–200mg+

Missed days (consecutive)	Dose	Dose Reduction
1–2	Any dose	No change
3–4	30 mg	No change
	31–60mg	Restart at 30mg or lower
	60mg+	50% reduction
5+	Any dose	Restart at 5–40mg

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<u>Initiation, Titration and Stabilization</u>

- A Starting dose of methadone is 30mg if the patient is at low risk of opioid toxicity.
    - Smaller doses may be considered in patients with unclear tolerance or at higher risk of opioid toxicity, such as those with concurrent sedative use
    - Some patients who have previously been on higher doses of methadone (>60mg) may be started at 40mg if at low-risk opioid toxicity (which is a practice in other provincial jurisdictions)
- Per guidelines, patients can increase their dose every 5 days if they have received 4-5 doses in a row.
    - In line with other provincial jurisdiction, standard of practice has shifted to allowing increases every 3 days if 3 doses in a row have been received
- Literature has shown patients typically stabilize on doses between 60-120mg. With the increased presence of fentanyl in the illicit supply, patients have required up to doses of 200mg in order to achieve stability due to increased tolerance.

<u>Missed doses</u>

- Guidance on missed doses based on consecutive days missed is described in the table on the righthand side.
- In those with low risk of opioid toxicity, patients may be restarted at 40mg rather

than 30mg.

Prescribing Methadone

- Typically prescribed as daily witnessed ingestion (DWI) in pharmacies
- Carry doses may also be an option for some patients
  - Clinical stability
  - Limited ability to travel to pharmacy

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- Daily witnessed ingestion is associated with significant reduction in methadone-related overdoses
- Carry doses can be considered in some patients
  - Clinical stability is defined as maintenance at stable dose of methadone for several months, evidence of concordant UDT, and evidence of psychosocial stability (no missed appointments, ability to store medication safely, supports return to work or school)
  - For patients in rural areas, travelling to pharmacy each day can be a significant barrier.

Prescribing Methadone

- Available in various formulations:

EXCEPTIONAL, LAST-RESORT

	Methadose (Mallinckrodt)	Metadol-D (Paladin)	Compounded methadone
Properties	Pink, cherry-flavoured, contains sugar	No colour, unflavoured, contains sugar	No colour, unflavoured, sugar-free
Concentration	10mg/mL	10mg/mL	10mg/mL
Formulation	Commercially concentrated	Commercially concentrated	Compounded by the Product Distribution Centre and delivered to the patient's pharmacy
Coverage	Regular PharmaCare benefit formulation. Covered under plans: B, C, G, P, W, and Fair PharmaCare.		Non-benefit, exceptional, last-resort coverage; determined on a case-by-case basis following trials of Metadol-D and one other methadone formulation.
Interchangeability[a]	✓	✓	✗
Additional notes	Described as "not having legs" by some patients; others may prefer this formulation.	Metadol is the same formulation but does not require dilution and is dispensed in hospitals instead.	From receipt of prescription, it takes ~48 hours to process and deliver the product to the dispensing pharmacy.

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- Pharmacare is a BC provincially funded program that helps cover pharmacy related and prescription medication costs for eligible patients.

2. Emergency Department Presentations

Missed Doses

- CAEP position statement recommends that administration of missed doses of OAT in the ED should be provided to support continuation of care
- This should be considered in patients who:
  - Have prolonged stay in the ED
  - Missed doses due to pharmacy closure

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Koh, J. J. *et al.* CAEP Position Statement: Emergency department management of people with opioid use disorder. *Cjem* **22**, 768–771 (2020).

Methadone Provision in the ED

- Doses provided in acute care do not appear on PharmaNet
  - Risk of double dosing if usual pharmacy not informed
  - Dose is marked as “missed” and may lead to dose reductions
- Prior to providing methadone, ensure the patient has appropriate tolerance and is not at risk of significant adverse effect
  - Check for respiratory illness, liver impairment, sedation
  - Check ECG for QTc prolongation if additional risk factors

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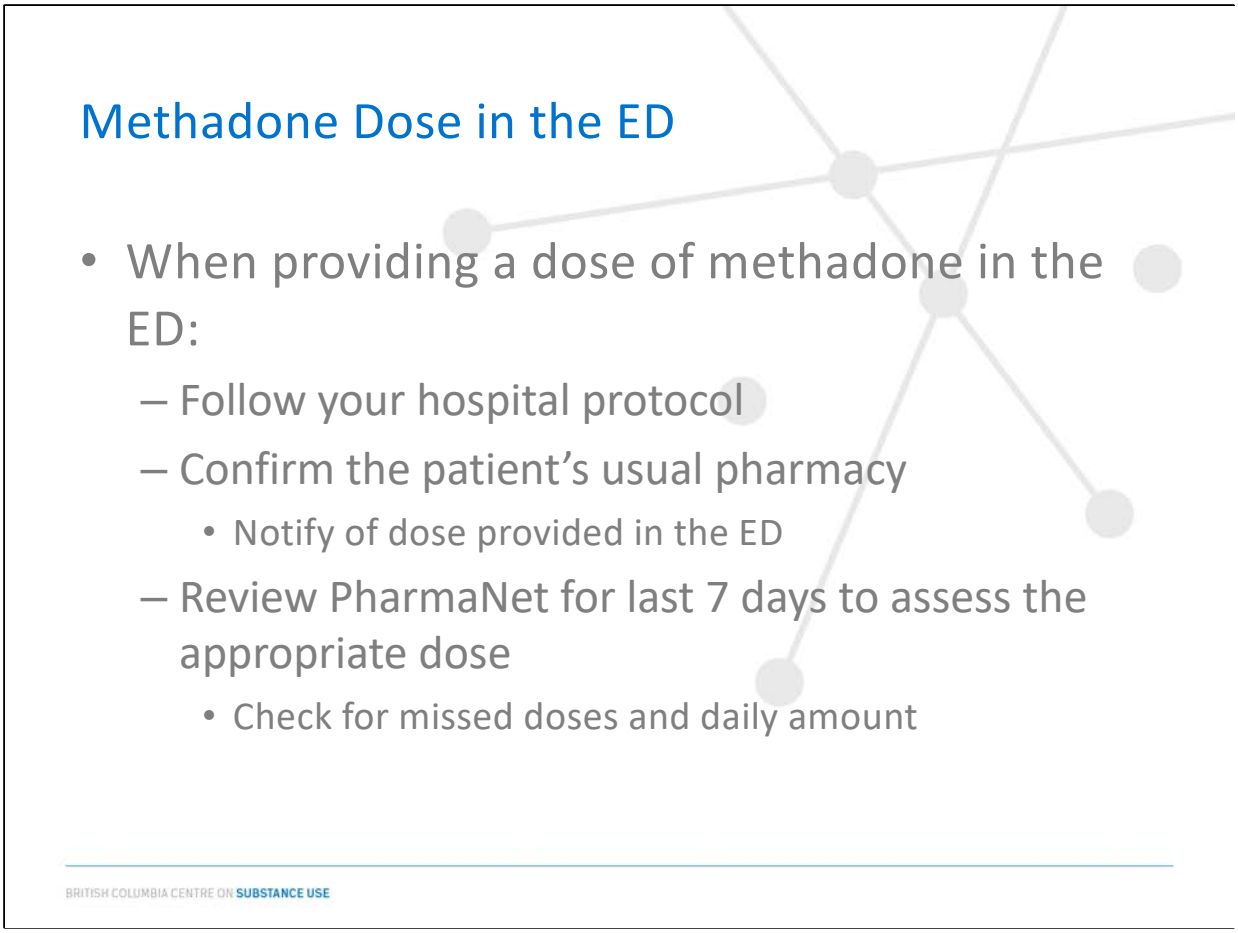
- PharmaNet is a province wide, central data system where any prescription dispensed in a community pharmacy will be entered. Healthcare providers can access this data system to review medication history and confirm any missed doses for opioid agonist therapy such as methadone.
  - Its validity is contingent of the pharmacist or a delegate entering the information.
  - Other jurisdictions may have similar regional pharmacy databases, and the approach would remain the same for providers.
- ECG is recommended in patients at high risk of QT prolongation, but not required prior to administration of dose of methadone in the ED



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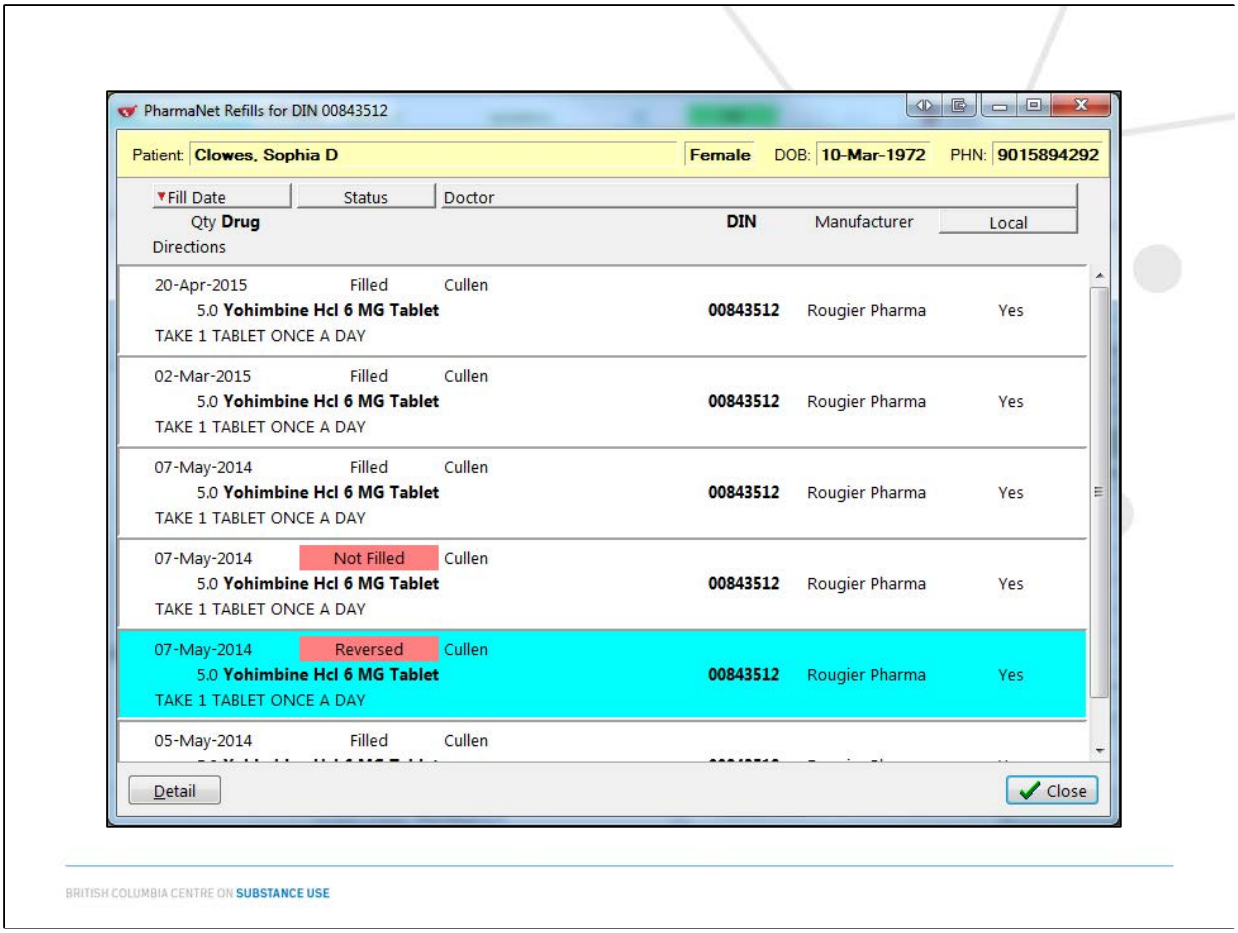
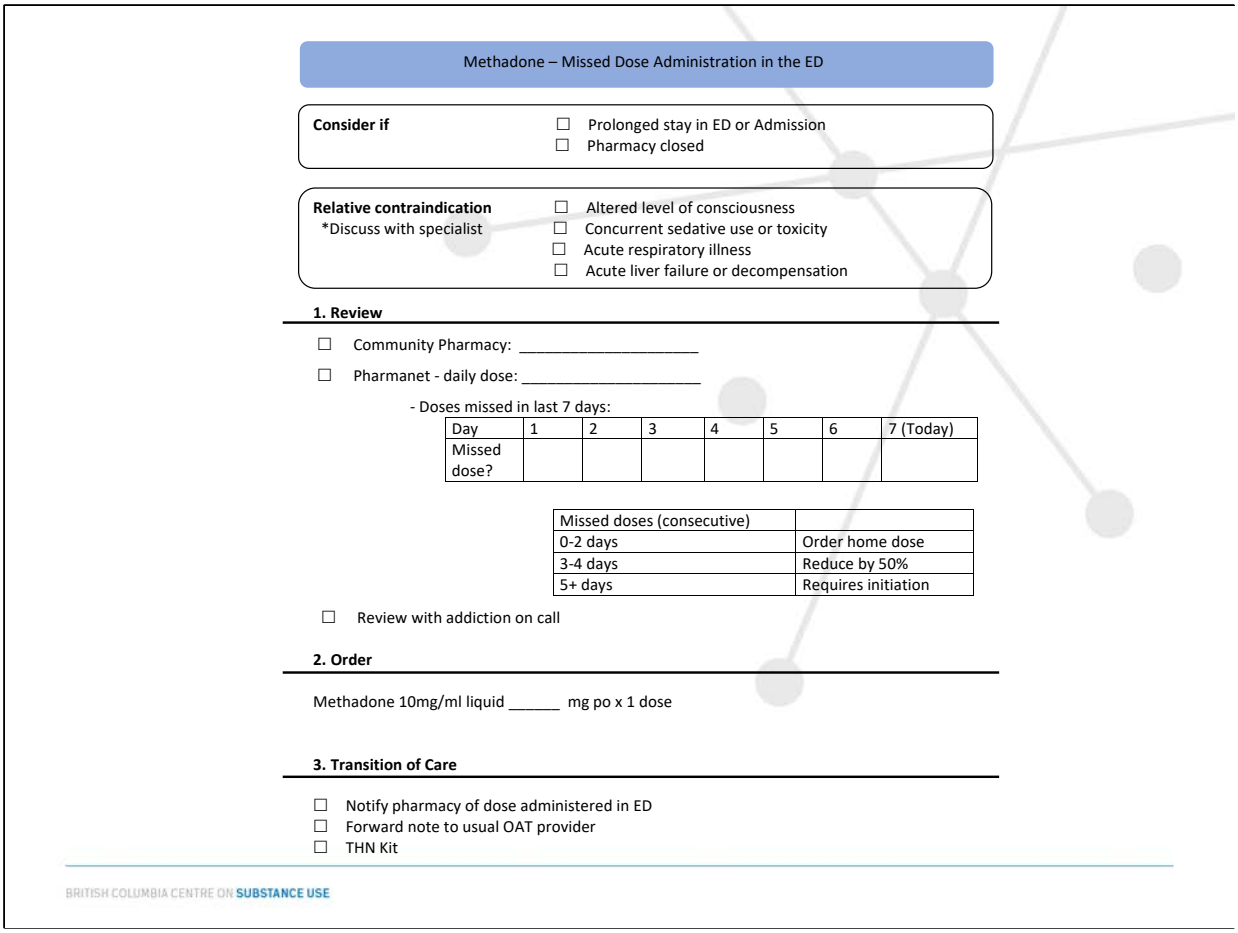
    - Its validity is contingent of the pharmacist or a delegate entering the information.
    - Other jurisdictions may have similar regional pharmacy databases, and the approach would remain the same for providers.
- Patients with carry doses may present more of clinical challenge, meaning they may have several doses that are unwitnessed. Consider seeking consultation with an addiction medicine specialist on how to approach these cases.



- This is a photo of how the doses will appear in PharmaNet.
- PharmaNet is a province wide, central data system where any prescription dispensed in a community pharmacy will be entered. Healthcare providers can access this data system to review medication history and confirm any missed doses for opioid agonist therapy such as methadone.
    - Its validity is contingent of the pharmacist or a delegate entering the information.
    - Other jurisdictions may have similar regional pharmacy databases, and the approach would remain the same for providers.
- For medications that are daily witnessed ingestions, each dose administered will be a separate entry
- Missed doses will be documented as either “reversed” or as a missing entry for that day.
    - Doses may only be reversed at end of day. If the patient’s usual pharmacy remains open, it is important to call and confirm with the pharmacy team directly whether a dose was administered or not in community.

Transition of Care

- Review harm reduction and safer use with the patient
  - Provide the patient with a THN kit
- Provide information about OAT clinics or low barrier clinics if patient not already connected to care
- Forward a note to the patient's usual provider about the dose received in the ED



Methadone – Missed Dose Administration in the ED

Consider if

- ☐ Prolonged stay in ED or Admission
- ☐ Pharmacy closed

Relative contraindication
*Discuss with specialist

- ☐ Altered level of consciousness
- ☐ Concurrent sedative use or toxicity
- ☐ Acute respiratory illness
- ☐ Acute liver failure or decompensation

1. Review

- ☐ Community Pharmacy: _____
- ☐ Pharmanet - daily dose: _____

- Doses missed in last 7 days:

Day	1	2	3	4	5	6	7 (Today)
Missed dose?							

Missed doses (consecutive)	
0-2 days	Order home dose
3-4 days	Reduce by 50%
5+ days	Requires initiation

- ☐ Review with addiction on call

2. Order

Methadone 10mg/ml liquid _____ mg po x 1 dose

3. Transition of Care

- ☐ Notify pharmacy of dose administered in ED
- ☐ Forward note to usual OAT provider
- ☐ THN Kit

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- This is an example checklist that can be used when providing methadone in the ED. **<u>This is not a formal PPO.</u>**

Methadone Initiation (1)

Refer to provider with expertise

- Initiating methadone requires:
  - Completion of POATSP
  - Prescription on harmonized prescription pad
  - More detailed assessment to candidacy of treatment, such as reviewing risk and benefit of initiation of therapy

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- POATSP (Provincial Opioid Addiction Treatment Support Program) is a comprehensive education and training program from the BCCSU (BC Centre on Substance Use) that provides the tools for providers in BC to prescribe oral opioid agonist therapy (buprenorphine/naloxone, methadone, and slow-release oral morphine) and injectable opioid agonist therapy.
- There are similar programs available in each province, where ability to prescribe certain oral opioid agonist therapies is contingent on completing this training.

Methadone Initiation (2)

- Assessment should include
  - Diagnosis of OUD
  - Determining tolerance and risk of opioid toxicity
  - Medication and co-morbidities review:
    - History of liver dysfunction, respiratory co-morbidity?
    - Concurrent sedative use?
    - Prior trials of OAT?
  - UDT recommended
- Consider barriers to continuation in community
  - Limited providers with capability to prescribe
  - Follow organizational referral pathways

•

Initiation—Special Scenario

- Consider initiation of methadone in high-risk patient where this might facilitate their stay
  - Prolonged stay in the ED or requiring admission
- It requires review with designated addiction specialist or a POATSP-trained provider
  - Contact local addiction consult team/specialist or 24/7 Addiction Clinician Support Line
- Use PPO for safety and monitoring
- Follow your hospital or health authority protocol

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- There are similar programs available in each province, where ability to prescribe certain oral opioid agonist therapies is contingent on completing this training.
- 24/7 Addiction clinical support line provides telephone consultation around substance use care to health care providers (physicians, nurse practitioners, nurses, midwives and pharmacist) in British Columbia.

Methadone Toxicity

- Methadone has a variable, prolonged half-life and bio-accumulation
  - This may lead to an insidious onset of symptoms
- Early signs of toxicity: ataxia, slurred speech, and "nodding off" (difficulty maintaining conversation)
  - If patient has prolonged naloxone requirement—consider screening for illicit use of methadone
- Onset of symptoms is typically within 9 hours of dose (mean: 3.2 hours)
- Treatment: Naloxone infusion (if naloxone is indicated)

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- Onset of symptoms should be considered for both prescribed and diverted methadone, and cases of accidental ingestion.

Hassanian-Moghaddam, H., Soltaninejad, K., Shadnia, S., Kabir, A., Movahedi, M., & Mirafzal, A. (2015). Risk Factors for Mortality and Endotracheal Intubation after Methadone Intoxication. *Basic & Clinical Pharmacology & Toxicology*, n/a–n/a. http://doi.org/10.1111/bcpt.12476

LoVecchio, F., Pizon, A., Riley, B., Sami, A., & D'Incognito, C. (2007). Onset of symptoms after methadone overdose. *The American Journal of Emergency Medicine*, *25*(1), 57–59. http://doi.org/10.1016/j.ajem.2006.07.006

Methadone Toxicity

- Factors that can lead to methadone toxicity include:
  - Sedatives
    - Prescribed or non-prescribed: gabapentin, benzodiazepines, antipsychotics, alcohol
  - Changes in tolerance
    - Acute medical illness
    - New medications
  - Rapid dose escalations
  - Recent discontinuation of medications that are cytochrome inducers (example: rifampin)

Gomes T, Juurlink DN, Antoniou T, Mamdani MM, Paterson JM, van den Brink W. Gabapentin, opioids, and the risk of opioid-related death: A population-based nested case-control study. PLoS Med. 2017 Oct 3;14(10):e1002396. doi: 10.1371/journal.pmed.1002396. PMID: 28972983; PMCID: PMC5626029.

Methadone Tolerance

- Methadone tolerance is highly variable
  - Within an individual
  - Between methadone and other opioids
- Tolerance in a patient can be impacted by:
  - Acute medical illness
  - New medications
- Cross tolerance with other opioids is unpredictable and highly variable
  - Conversion ratio with morphine varies beween 1:4–1:12+
  - Conversion between opioids and methadone is **not recommended** in the ED

Tolerance and Acute Medical Presentation

Tolerance prior to hospital ≠ tolerance in hospital

- ↓ tolerance to metabolism of methadone
  - Sepsis
  - Liver failure
- ↓ tolerance to peak effect of methadone (sedation)
  - Respiratory failure or decompensation
  - Concurrent sedatives – management of alcohol withdrawal

- Tolerance to methadone can vary in two different ways: the ability to tolerate metabolism of methadone and the ability to tolerate peak effect.

Methadone and Opioid Withdrawal

- Opioid withdrawal can occur prior to the next dose or several hours after a dose
- Withdrawal may result from:
  - Inadequate dose (<60–80mg)
  - New diagnosis
    - Pregnancy (2nd and 3rd trimester)
  - New medications
- If opioid withdrawal is present, consider treatment with IR opioids to temporize in the ED

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See module on withdrawal management

QT Prolongation and Methadone

- Risk increases at doses >100mg
- Most cases of torsades occur with QTc>500
- Consider ordering an ECG if administering QT-prolonging agents to a patient who is on methadone
- If a prolonged QTc (>500) is present:
  - Rule out other causes (e.g., electrolyte derangements)
  - Hold methadone and treat with IR opioids

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Methadone is an independent predictor for developing torsade the pointe by prolonging QTC through its inhibition of HERG potassium channel. The risk of cardiac arrhymia significantly increases at doses greater than 100 mg, and most cases of Torsade de pointe due to methadone occur at QTcs greater than 500.

•If you need support managing precipitated withdrawal, inducting a patient on to buprenorphine/naloxone, or providing any other aspect of addiction and substance use care, you can call the 24/7 addiction medicine support line.

• The 24/7 addiction medicine clinician support line provides telephone consultation for physicians, nurse practitioners, nurses, mid-wives, and pharmacists who provide addiction and substance use care. It is available 24/7, 365 days a year. The number to call is 778-945-7619. More information can be found at www.bccsu.ca/24-7.

Provincial Opioid Addiction Treatment Support Program

- The Provincial Opioid Addiction Treatment Support Program contains modules with more information on opioid use disorder and opioid agonist treatments, including buprenorphine/naloxone. This program is available online and it is free of charge.

References

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