Methadone Maintenance:
Strategies to Improve Safe Prescribing and Dispensing

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Learning Objectives

- Utilize current methadone safety guidelines
- Explain safety implications of methadone dosing changes
- Employ patient counseling strategies on the safe use of methadone

Outline

- Methadone Maintenance Treatment
- Methadone Pharmacology
- Risks
- Risk Mitigation
  - Safe Prescribing
  - Diversion Prevention
  - Accidental Exposure Prevention
  - Effective Communication
Case

- 25-year-old single female attends a methadone program to get onto methadone!

History:
- Hurt her back at work 4 years ago
- Started with NSAIDs, went to acet/codeine/caffeine #3 and then oxycodone/acet
- Worsening pain – switched to sustained release oxycodone 80 mg po bid
- Smokes 30 cigarettes per day
- Drinks 2 to 15 standard drinks per week
- Diagnosed with MDD

Case, cont’d

- She attends an abstinence-based treatment program and stays drug-free for 2 years. However, she has relapsed again for the past year to opioids, cocaine, THC, and alcohol
- She mentions that she has been amenorrheic (no periods) for 6 months ever since she began snorting “oxys”
- She has been having unprotected sex with men, but does not believe she is pregnant
On Examination

- In acute withdrawal
- Urine toxicology confirms presence of 6 MAM and morphine, THC, and BEG
- Vitals are stable
- How will you explain the treatment options to the patient?

Pharmacological Options

Methadone

- Long-acting oral opiate analgesic
- Given in the appropriate dose to opioid-dependent patients
  - Suppresses symptoms of withdrawal
  - Reduces craving for opiates
  - Does not induce sedation or euphoria
  - Cross-tolerance to other opiates


Benefits of MMT

- Decreased illicit drug use
- Decreased criminal activity
- Improved employment rates
- Improved psychological status
- Decreased mortality (11 times)

Relative Success Rate of MMT to Detox

- Cochrane Review: Meta-analysis of 6 RCTS, n=954
- Methadone significantly more effective in retaining patient in treatment
  \[ \text{RR} = 3.05; \quad 95\% \text{CI}: 1.75-5.35 \]
- Methadone significantly more effective in the suppression of opioid use
  \[ \text{RR} = 0.32; \quad 95\% \text{CI}: 0.23-0.44 \]


Completion of Treatment

Abstinence 2.5 years after tapering:

<table>
<thead>
<tr>
<th>Therapeutic taper</th>
<th>42%</th>
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<tbody>
<tr>
<td>Drop out, involuntary</td>
<td>7%</td>
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- Do not pressure patients to taper!
- Long-term methadone users (>2 years)
- More successful than short-term users

Methadone Pharmacokinetics

- Fully absorbed within 1/2 hour
  - Bioavailability can range from 35% to 100%
- Serum levels peak in 2 to 4 hours
- Biotransformed in the liver
- CYP3A4, and also CYP2B6, CYP2D6, CYP1A2
- Half-life between 24 and 36 hours; up to 55 hours

+++ interindividual variation = +++ variability in responses


Risks

Less Common
- QTc prolongation

Common ADRs
- Sedation
- Constipation
- Sweating
- Weight gain
- Sexual dysfunction
- Insomnia

Respiratory Depression (dose-related)
Overdose Risks

- For nontolerant adults, a single day's maintenance dose of methadone 50-100 mg can be lethal.
- For people beginning MMT, starting doses of as little as 40 mg have led to deaths after 3 days of treatment.
- The lethal dose is lower if it is taken with other opioids, alcohol, benzodiazepines, or barbiturates, or other drugs.


Opioid-Related Deaths in Ontario

![Graph showing the manner of death per opioid type.](image)

Figure 1. Manner of death per opioid type. This graph illustrates the relative proportion of accidental, suicide, or undetermined manner of death per opioid type. The graph represents all single opioid-related deaths in Ontario, Canada between the years 2006 and 2008 (n= 1940 deceased).
Case

- Approval is granted to start the patient on methadone
- What are some of the risk mitigation strategies during the induction period?

Safe Prescribing

- Slow Titration
  - Start low, go slow, and monitor closely
  - No clear relationship between reported use (e.g., “heavy use”) of heroin or other opioids and the final methadone dose
  - **Initial dose:** 10-30 mg
  - Increase dose by 5-15 mg q3 to 5 days if patient reports withdrawal or strong cravings
  - Above 80 mg or in maintenance phase, increase 5-10 mg every 1 to 2 weeks
Safe Prescribing

Identification of High-Risk Patients
- Higher-risk individuals: lower starting range of 10-20 mg (5-10 mg if recently abstinent with negative initial urine)
  - Recent benzodiazepine use
  - Use of other sedating drugs
  - Alcohol-dependent patients
  - Aged older than 60 years
  - Respiratory Illnesses
  - Taking drugs that inhibit methadone metabolism
  - Lower opioid tolerance
  - Decompensated hepatic disease
  - Recent discharge from inpatient rehabilitation facility
  - Recent incarceration

Safe Prescribing

Drug Interaction Awareness
- Pharmacodynamic
  - Additive QTc prolongation
  - Additive sedation
- Pharmacokinetic
  - Altered methadone concentrations
Safe Prescribing

- Drug Interaction Awareness
  - Overmedication reactions are likely due to CYP inhibition that develops quickly within a few days after concurrent drug administration
  - CYP induction is slower to emerge, commonly taking approximately a week to produce significant withdrawal signs/symptoms
    - In the presence of strong CYP inducers, merely increasing the methadone dose may be insufficient, and an increase plus more frequent daily dosing may be necessary


Case

- Patient presents to the pharmacy once at 100 mg/d, but has missed 3 days of her medication
- Is irritable and demanding
- What will you do to help this patient stay engaged in treatment?
- What are some of the risk mitigation strategies?
Safe Prescribing

- Managing Missed Doses
  - Tolerance to opioid effects is lost quickly when opioid stopped
  - Need to adjust dosing with just 3 days of missed dosing
    - Only 2 days if in early stage of treatment and still stabilizing dose

Diversion Prevention

- Dilution of Oral Solution
  - Large dilute volumes in a vehicle other than water serve as a deterrent for injection drug use
  - Recommended that methadone solution is dispensed in juice to a volume of 100 mls per dose
    - For both observed and take-home doses

- Only commercially available 10-mg/mL oral preparations are permitted for use as stock solutions in most provinces (eg, New Brunswick)
**Diversion Prevention**

- **Observed Dosing**
  - Daily oral dose administered at pharmacy
    - Witnessed ingestion of methadone solution
  - Ensure entire dose swallowed – have patient talk afterwards
  - Particularly at start of treatment until gain clinical stability

- **Take-Home Doses ("Carries")**
  - Not recommended in first few months of treatment
  - Consider:
    - Is it safe for the client?
    - Is it safe for the public?
    - What is the risk of diversion?
Diversion Prevention

- Risks Associated With Diversion
  - Intoxication or overdose from taking multiple doses
  - Patients diverting all or part of their carry doses for a period, and then having to ingest the full dose (eg, in the pharmacy or while hospitalized), could overdose because of decreased tolerance

Accidental Exposure Prevention

- Safe Storage
  - Children may overdose by mistaking the medication for a drink. A dose of 10 to 20 mg methadone can be fatal to a child
  - Store take-home methadone doses in a locked box in a refrigerator (eg, lockable fishing tackle box), especially in households with children

Accidental Exposure Prevention

- Prescription Tracking
  - Ensure prescriptions do not overlap
  - Indicate exact days for dosing
  - Indicate observed or take-home doses

Accidental Exposure Prevention

- Accurate Dispensing
- Special care must be taken in measuring concentrated formulations (10 mg/mL)
  - Measured doses should be double-checked and double-signed against the original prescription, whenever possible
- Must use devices able to deliver small (ie, 0.1-mL) increments
  - Graduated cylinders and certain syringes may not be appropriate for this purpose
- Even small measurement errors may be clinically significant

Effective Communication

- Between Prescribers and Pharmacists
  - Open communication required!
  - One pharmacy makes communication easier
  - Work out policies re:
    - Intoxication
    - Missed doses
    - Carry requests

Effective Communication

- During Transitions in Care
  - Double-dosing or dosing after tolerance is lost can occur:
    - when patients move from hospital or from prison back to their usual pharmacy
    - when patients switch from one community pharmacy to another
  - Always confirm the quantity and timing of the last dose to ensure that clients receive the appropriate dose
Patient Counselling Points

- Inform Patients:
  - Of risk factors for, and signs and symptoms of, intoxication and overdose
  - To immediately seek medical assistance if intoxication occurs
  - That they will not be medicated if they present intoxicated, because of safety concerns
  - That take-home medications must be kept in a secure place (eg, in a locked box) out of reach of others, particularly children
  - To let their healthcare providers (eg, pharmacist, physician) know if they have missed any doses or taken any additional ones
  - That after each dose increase, it may take 3 days or more to experience the full benefit of the dose increase. Encourage them to refrain from using extra doses and to be vigilant for signs of sedation
  - Of the risk for overdose if they take methadone with other opioids, alcohol, benzodiazepines, or barbiturates, or other sedating drugs

Summary

- Methadone is a life-saving medication that should be administered chronically
- The risk for overdose occurs mainly during induction, co-administration of other medications, because of dilution errors, and via double-dosing
- Good practices by providers and patients lead to very good outcomes and can be managed by education, SOPs, and adherence to CPGs
Resources

- Opioid Dependence Treatment Certificate Program
  http://www.camh.ca/en/education/about/AZCourses/Pages/ODT_Certificate.aspx

- Opioid Dependence Treatment Core Course
  http://www.camh.ca/en/education/about/AZCourses/Pages/odtcore_odt.aspx

- College of Physicians and Surgeons of Ontario Methadone Maintenance Treatment Program Standards and Clinical Guidelines 2011

- www.methadonesaveslives.ca

- For a list of drugs that inhibit or induce metabolism of methadone, please visit the following URL:
  http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3334287