Methadone treatment for people who use fentanyl: Using case discussions to explore the META:PHI guidelines

META:PHI CONFERENCE 2021

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META:PHI
MENTORING, EDUCATION, AND CLINICAL TOOLS FOR ADDICTION
PARTNERS IN HEALTH INTEGRATION

Disclosures

Lisa Bromley - I have a relationship with a for-profit and/or a not-for-profit organization to disclose.

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Anita Srivastava -

Off-label Use

We will be discussing off-label use of slow-release oral morphine (Kadian, SROM)

Agenda

- Introductions
- Reflections on OAT and the METAPHI guidelines from the perspective of lived experience
- Overview of the META:PHI guidance document: Methadone treatment for people who use fentanyl
  - Rationale
  - Guideline development
  - Underlying principles
  - Key recommendations
- Case discussions 3 x 20 min
- Wrap up panel

Schedule

- 1:15 -1:55 - Introductions
  - Methadone – lived experience (Andrew)
  - Review of the METAPHI guideline
  - Reflections on the guideline (Andrew)

- 1:55-2:15 – Case x 1
- 2:15-2:30 – Break
- 2:30-3:10- Cases x 2
- 3:10-3:30 - Wrap up panel

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Acknowledgements

- We acknowledge that we do not represent the diversity and scope of patient or provider communities
- We encourage participants to identify the experiences and lenses that they bring to this work and to challenge themselves to consider other perspectives, specifically those of individuals from BIPOC communities, LGBTQ+ communities, and those who have experienced trauma (including medical trauma, ACEs and stigma)
- We acknowledge that being patient centered means including the perspectives of people with lived experience in their treatment decisions as well as in program planning, guideline development and education of healthcare providers. People with lived/living expertise of OUD were involved in the review but not the writing of the guideline described in this presentation.

Andrew

Background

- Presence of fentanyl and fentanyl analogues in the illegal opioid supply across Canada have been associated with devastating overdose rates
- Existing guidelines at the time of this project (CPSO 2011, since rescinded) created barriers to treatment for all patients with OUD
- People who use fentanyl have far higher opioid tolerance than accounted for in the 2011 MMT guidelines and are also at significantly elevated risk of overdose
- Recommendations to start and titrate doses conservatively, combined with requirements for frequent visits for re-assessment and renewal of prescriptions make it difficult for patients to achieve therapeutic methadone doses and want to engage in OAT
- Guideline group: Lisa Bromley, Mel Kahan, Lori Regenstreif, Anita Srivastava, Jennifer Wyman with Sarah Clarke

Guideline Development

- We conducted focused literature searches on evidence for methadone in people who use fentanyl, methadone initiation and titration protocols, optimal dosing, methadone safety and treatment retention
- We achieved consensus amongst ourselves
- The guidance document was reviewed by three groups, whose feedback was incorporated into the final version:
  - Invited reviews from clinicians working in different health disciplines and settings
  - Anonymous reviews from members of the META:PHI Google Group
  - Focus group comprised of people with lived/living expertise and family members

Underlying Principles

- Clinical decisions should have the overarching objective of promoting patient engagement and retention in treatment
- The risks of a subtherapeutic methadone dose are substantial: a patient who remains at or around 30 mg is at high risk of treatment drop out and fatal overdose
- The risks of iatrogenic methadone toxicity are low when prescribed carefully, and substantially lower than the risk of overdose with street supply opioids
- Caution is required due to the pharmacology of methadone; dose increases are limited in quantity and frequency by bioaccumulation of methadone, which can be fatal in the first two weeks of treatment
- All other clinical decisions should be based on clinical judgment

Methadone may be preferable to buprenorphine for patients at high risk of treatment drop-out

- Methadone and buprenorphine are both first-line OAT options
- Methadone should be considered as a first option for:
  - Patients who have done well on methadone in the past
  - Patients who do not want or have not benefited from buprenorphine
  - Patients for whom buprenorphine has not been successful

- Studies have consistently shown that methadone has higher treatment retention rates than buprenorphine (average retention rates at 4 and 6 months 73.9% and 74% for methadone, 45.9% and 46% for buprenorphine, Timko, 2016)
- Methadone appears to protect against overdose even among patients who continue to use fentanyl
- In a 6-month study of 127 fentanyl users on methadone, there were no deaths, although 4 people died shortly after dropping out of treatment (Stone, 2020).

Attempt to reach an optimal dose of methadone safely and effectively

- People who use fentanyl are more likely than people who use prescription opioids to drop out of OAT (Arfken, 2017)
- Historic recommendations advised clinicians to aim for doses of 60mg or above; these doses are too low for people using fentanyl based on known MMEs.
- While calculations vary, the following equivalencies are derived from Safe Supply program documents (Griffith et al, 2021) and the BCCSU iOAT guideline:

1pt fentanyl IV ≈ 32-48 mg hydromorphone IV ≈ 64-96 mg hydromorphone po

≈ 320-480mg morphine po

≈ 60 mg methadone

- Flexible dosing (i.e. titrated to suppress withdrawal symptoms and cravings) is associated with lower rates of ongoing use based on self-reports and urine drug screens (Kakko, 2007, Beck, 2014)
- Doses above 100mg are recommended for people who use fentanyl regularly as long as they are not experiencing sedation or side effect

Starting methadone at 30mg is recommended

- Higher starting doses can help shorten the trajectory to achieving therapeutic levels
- We recommend 30 mg even when UDS shows BZDs due to the prevalence of BZDs/analogues in the street supply, unless the patient has demonstrated BZD toxicity or is at increased risk of methadone/BZD toxicity (COPD, elderly, ETOH)
- Why not 40mg or higher?
- Deaths during the first week of methadone have been reported at doses above 30mg
- Multiple studies have shown that the majority of overdose deaths for patients on methadone occur in the first two weeks of treatment (Leece, 2015)
- Methadone metabolism is primarily related to CYP2B6; half-life is longer on initiation and declines with induction of the enzymes that metabolize methadone
- Despite high opioid tolerance among people who use fentanyl, cross tolerance to methadone is incomplete and variable

Focus Group Feedback

- Consensus of the focus group was that 30mg is too low to make a significant impact on withdrawal symptoms among people with high opioid tolerance and that experience with substantially higher doses (e.g. from carries) have not caused them to overdose
- The group favoured starting doses in the range of 40-60mg
- The authors acknowledge that there are settings in which 40mg is used as a starting dose and that future versions of the guidance document should seek new evidence for higher starting doses
- Adding slow-release oral morphine to methadone is suggested as a strategy to help augment initial methadone doses

SROM may be co-prescribed with methadone and maintained or tapered depending on clinical response

- Approach adapted from the 2008 Saskatchewan methadone guidelines
- SROM can be used alongside methadone because there is no bioaccumulation of morphine; steady state is reached within about 2 days
- Can be initiated on the same day as methadone, e.g. 30mg methadone + 200mg SRM
- Suggested initial dose range 50-300mg (CPSS recommended maximum starting dose 200mg)
- SROM should be used with extreme caution in a patient with renal insufficiency
- Risks of toxicity should be measured against the potential benefits of reduced fentanyl use
- ***Rx as: "Witnessed dose daily with methadone. Open capsules and give sprinkles in cup, swallow with methadone"***

Titrate OAT faster in those not at high risk of toxicity

- Methadone can be increased by 15mg every 3-5 days , e.g. 30->45->60->75 on day 10.
- Once a dose of 75-80mg is reached, the dose can be increased by 10mg every 5-7 days
- We do not recommend slowing methadone titration for people using prescribed or illicit benzodiazepines unless the patient has demonstrated BZD toxicity or is at increased risk of methadone/BZD toxicity (COPD, elderly, ETOH)
- Patients who have recently been on methadone can be considered for more rapid dose increases based on their tolerance
- SROM can be titrated along with methadone in increments of 50-100mg
- Assessment for withdrawal symptoms and sedation is advisable prior to a dose increase
- Assessments can be conducted in-person or by telephone or video

Methadone doses of 100mg or higher are typically required

- Doses above 100mg are recommended for people who use fentanyl regularly as long as they are not experiencing sedation or side effects
- Methadone dose increases should not be delayed if clinically indicated and an ECG is not available
- ECG screening is advised for patients on doses of 150mg or more, who are at increased risk of arrhythmias due to cardiac conditions or QT-prolonging medications (Haddad, 2002)
- There is no target SROM dose; previous protocols suggested tapering SROM once patients had stabilized on methadone, but a subset of patients may remain on combination methadone + SROM (expert opinion)
- Adding or increasing SROM alongside methadone may be appropriate when an EKG is warranted but not available and further titration of OAT would be beneficial for the patient

Focus Group Feedback

- Participants stated that 120mg is the minimum dose necessary to reduce fentanyl use
- They emphasized that rapid dose escalation is important motivation for people who use drugs to make the effort to obtain methadone rather than readily available fentanyl
- The authors acknowledge that while the titration protocol recommended represents a change from previous guidelines it may not be rapid enough to meet the goals of people who use fentanyl
- SROM may be helpful
- Future versions will consider evidence for the safety of more rapid outpatient titration protocols

Patients who miss methadone should be assisted to resume previous doses quickly and safely

- In contrast with previous guidelines, we do not recommend cancelling methadone prescriptions unless the patient has missed 4 consecutive doses.

Days missed	Dose	Increases
Three (patient presents on day four)	Continue previous dose; no adjustment required	10–15mg every three days as per usual titration protocols
Four (patient presents on day five)	The higher of 50% of previous dose or 30mg	10mg daily for three days (not exceeding the most recent dose), then reassess and proceed as usual
Five or more (patient presents on day six or later)	Restart: 30mg +/- SROM maximum 200mg	10–15mg every three to five days

- Adjustments for SROM follow a different schedule: BCCSU guidelines recommend a reduction of 40% after 2 missed doses, 60% after 3 missed doses and 80% after 4 missed doses – but consider in light of SROM starting dose (max 300mg)
- It is important to communicate this change to the pharmacist to ensure that prescriptions are not cancelled per previous guidelines

Dose titration in the context of missed doses

- Consider dose increases for patients who repeatedly face challenges achieving 3 consecutive doses, particularly those who have previously demonstrated tolerance to methadone and high-potency opioids in the following situations:
  - At or under doses of 60mg
  - If the patient has had at least 4 doses in the past 5 days (i.e. non-consecutive)
  - Patient reports little withdrawal relief at the current dose
  - Continuing fentanyl use
  - Lack of sedation

- We do not recommend an increase if the patient has just missed a dose; continue the previous dose until 4 of 5 doses have been consumed and then increase. A prescription for a planned dose increase can be written with instructions to the pharmacist to assess for sedation
- Patients should be seen before a second dose increase
- Use clinical judgement in presence of benzos+ or patients you don't know well

Take Home Doses – Methadone

- Consider take-home doses with caution due to risks to patients and community. Assess the benefits of carries to the patient as well.
- Minimum ***one month*** observed daily dosing before starting carries
- Base decisions primarily on a clinical assessment of stability and an individual's ability to manage carries safely:
  - Housing and ability to store medication
  - No ongoing high risk use e.g. recent overdose, intoxication or sedation at assessment, unstable psychiatric conditions, regular IVDU
- Non-consecutive carries may be utilized with patients who use substances (including opioids) in ways that are not high-risk
- Take-home doses with SROM generally follow a much more conservative approach per the BCCSU guidelines due to the risks of large quantities of injectable morphine

Focus group feedback

- Participants felt that carries should be provided almost immediately to make methadone more compelling than fentanyl. Participants also felt carries are essential for people to work and live their lies and should be based on trust and not urine samples. They strongly disagreed with the notion of carries as contingency management.

- The authors agree that decisions about carries should be made based on ongoing evaluation of their benefits relative to risks for the individual, as well as the risk to the public from diversion. While the document does not recommend initiating carries at the onset of methadone treatment, the recommendation to base decisions on clinical judgement creates substantial flexibility.

Adopt practices which promote treatment retention and harm reduction

- Practice a trauma-informed approach to care
- Base frequency of visits on clinical need and decision-making ***not*** on fixed schedule (e.g. stable doses = monthly) or the "need" for a urine screen
- Use video/phone assessments for patient who miss in-person appts
- NEVER stop a methadone Rx for a missed appointment without assessing further. If a patient is dosing regularly, continue their Rx and ask the pharmacy to remind the pt to see MD
- Partner with pharmacists to assess patients and maintain continuity & communication
- For established patients who repeatedly miss doses or appointments, consider leaving a prescription for methadone 30mg that can be released as long as the patient has not missed 7 consecutive days of methadone
- Provide treatment for concurrent psychiatric and medical conditions
- Partner with other agencies to support additional need such as housing, disability
- Offer education, naloxone kits and harm reduction counseling, supplies and supports

Urine drug testing

- Urine drug testing should not be required for a prescription to be released, for an appointment or for dose adjustments
- The limitations of UDS include false positives and false negatives, especially for benzodiazepines
- Frequency of samples can be a discussion between clinicians and clients; when a therapeutic relationship exists and clinical stability has been established, urine samples are less relevant.

Focus group feedback:

The group felt strongly that urine samples should never be supervised. They reiterated the importance of an honest relationship between patients and providers. Specific comments were that “we need to stop punishing people who use drugs by deciding their course of treatment off their urine sample results”.

Andrew

Case #1

Roger, 50Y M

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Case 1- Roger

- 50 yo male at your MMT clinic on and off x 3 years
- Last stable on methadone without opioid use about 2 years ago
- Currently living mostly at a shelter & using large amounts of fentanyl IV daily
- Recently attending the clinic very intermittently; more missed doses than not
- Clinic staff message you that he came by asking to restart methadone but left before being seen; he reported using 1gm of fentanyl/day
- What would you do?

Roger

- You sent a prescription for methadone 30mg + SROM 200mg x 7 days to the pharmacy
- Roger missed one dose; he has not made it back to the clinic for assessment. He is now at the pharmacy looking for a dose. The pharmacist calls you asking for advice.
- What would you do? Would you continue his dose? Increase it?
- Does it matter which dose he missed?
- How many times would you extend the Rx for a starting dose without Roger attending your clinic in person and doing a urine test?

Roger

- You continued the prescription for methadone 30mg + SROM 200mg for another 7 days
- Roger comes in the following week on Wednesday.
- He took his methadone 30mg and SROM 200mg on Friday & Saturday, missed Sunday, and dosed again Monday and Tuesday.
- He is alert and slightly agitated. He states that he barely feels his OAT – it lasts for about an hour after his dose. He is using large amounts of fentanyl the rest of the day. He asks you for a dose increase.
- What would you do?
- What if he missed Sunday and Monday?

Roger

- You increased the dose of methadone to 45 mg on the day of assessment. SROM remained the same at 200 mg
- Roger has been getting his doses regularly and his methadone is now at 70mg with SROM 300mg.
- You increase his methadone to 80mg and keep the SROM the same.
- He has one dose of 80mg and then misses 3 days in a row.
- What would you do about his methadone and his SROM?
- What if he missed 4 consecutive days?
- What if he missed 5 consecutive days and presented on Day 6?

Roger

- Roger has been back on methadone for one month. He is on methadone 120mg + SROM 300mg. He continues to use fentanyl but not every day.
- He wants to go visit his brother in a different city one hour away because his brother has been in a traumatic accident. There is no pharmacy within 30 minutes of his family's home in a more rural area. Roger is requesting one carry (take home dose) to make this trip.
- What would you do?

Roger

- Over the next month Roger has attended fairly regularly and his dose is now 120 mg methadone + 300 mg SROM.
- He misses an appointment with you and presents to the pharmacy on day 4 after 3 full days of missed doses. The pharmacist calls you for your recommendations. He says Roger is alert but slightly agitated, restless, and impatient. He is hoping to get a dose of OAT.
- What would you do?
- What if he had missed 4 full days and presented on day 5?

Case #2

Jim, 41Y M

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Case 2- Jim

- 41yo on 130 mg methadone
- Stable for 4 years, 6 carries for 3.5 years (13 since COVID)
- Previous drug of choice oxycodone PO, snorting
- Issues with alcohol in the past; abstinent x 3 years
- Previous crystal meth use – very intermittent, mostly work-related
- Healthy, on citalopram 20mg OD for 3 years
- Seen by you for first time today, moved from previous town last week

Case 2- Jim

- Lost his job during COVID
- Had to move to find cheaper housing and work
- Moved on long-weekend
- Usual carry pick up day is Saturdays
- Missed dosing and pick up Saturday due to the move
- Went to new pharmacy Sunday (old pharmacy closed Sundays and could not contact prescriber)
- Significant withdrawal symptoms by Sunday night and sought HM tablets and fentanyl

Case 2- Jim

- Booked into your RAAM clinic on Tuesday morning (initial visit)
- Last witnessed dose of methadone was the Saturday before (9 days ago), when he picked up 6 carries
- Reports drinking last carry dose on Friday (missed Sat/Sun/Mon)
- You have pharmacy records verifying carry status and dose
- He reports using 1-2 points of fentanyl and several 8mg HM tablets over 2 days
- He has to be at his new job at a packaging plant by 1 pm

Case 2- Jim

- UDS positive for HM, fentanyl and EDDP
- What dose of MMT?
  - Issues:
    - LWD was over one week ago
    - Has missed 3 consecutive doses
    - Recent use fentanyl

Case 2- Jim

- New guidance:
  - Missed three consecutive doses can dose full dose (130mg) on Day 4
  - Caution in this case with discussion regarding how he was using carry doses (daily vs missing doses and doubling up etc)

- You continue his prescribed 130 mg methadone and ask Jim to stay for 3 hours so you can ensure not sedated at peak dose
- Jim thinks this might make him late for work so you agree to call his cell phone to check in with him
- He's worried that having to go to the pharmacy every day will make him late for work also. He wants to know if he can have carries?

Case 2- Jim

- Jim follows up five days later and is still in significant withdrawal in the evenings. He is struggling to avoid fentanyl. His goal is abstinence.
- He has been getting all doses at the pharmacy every morning before his shift
- He is wondering if he needs a dose increase (currently at 130mg)
- What are your considerations?
- How much will you increase his dose?
- What about carries?

Case 2- Jim

- You increased his dose to 140mg and see him the following week
- He has been able to reduce his fentanyl use in half and is no longer using HM tablets
- He is encouraged that he is feeling better but not quite out of withdrawal when he stops fentanyl
- He has not had an EKG done
- What would you do next?
- What if he disclosed that he is using meth again?
- What if he reported that alcohol use has resumed in conjunction with the stresses around all of this?

Case 2- Jim

- Follow up with Jim 1 week later, he reports feeling well at 145 mg and no longer using any other opioids; he got ECG (QTc = 442)
- What if he were not doing well and he had not gotten an EKG?
- What if he were not doing well and his QTc was 495?

Jim

- Jim is wondering when he can get the rest of his carries back as driving to the pharmacy before work is adding an hour to his day
  - Discussion:
    - 3.5 years sobriety, brief period of substance use
    - consider individual risk factors/supportive factors (new job, stable relationship, housing etc)

Case 2- Jim Summary

- Dosing patients with carries with last witnessed dose occurring remotely in time
  - Consider assessments at peak dose (importance of flexibility, can use telemedicine)
- Dose increases over 130mg without an ECG – more important to increase dose when fentanyl is being used (risk of overdose > risk of theoretical QTc prolongation)
- Carry rules and reinstatement – more flexibility now, more diverse definitions of stability and "success"
  - Stability viewed holistically (knowledgeable relationship with patient, protective factors, risk factors)
- Limitations of pharmacotherapy – importance of understanding patient's context (not only results of urine drug testing)

Case #3

Maria, 36Y F

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Case 3 – Maria

- 36yo female new to you. She comes in asking to be started on methadone because she has been on buprenorphine twice recently and didn't feel it was helpful. Two years ago in her hometown she was on methadone 110mg a day and she would like to go back on methadone because she felt it worked better for her.
- Substance Use:
  - 2-4 points of fentanyl iv daily
  - $10 worth of crystal meth daily
  - 6-8 tall cans of beer daily
- Medications: gabapentin 300mg TID
- UDS: positive for fentanyl, buprenorphine, benzos, and amphetamines.
- Lives alone
- What would be a reasonable starting dose of methadone for her?
- Is there anything else you want to know or do?

Maria

- You start her on methadone 20mg and SROM 200mg.
- She returns four days later (Day 4) and appears very tired during the visit but says she just had a rough night and didn't sleep well. Her pupils are pinpoint and she nods off twice in mid conversation. She took her methadone and kadian Days 1-3 but hasn't had her dose yet today. She stated she used some fentanyl in the early morning hours before coming to clinic. She is asking you to increase her methadone dose because she says she can barely feel it and she knows she needs a much higher dose and all her friends were started at 30mg.

- The clinic is not open the next day and it is a long weekend.
- How would you proceed today? Would you hold her dose? Increase her methadone?

Maria

- You increased her dose to 30mg methadone and kept her kadian at 200mg. You asked her to go to the pharmacy when she was more alert. You spoke with the pharmacist to convey your concerns and ask them to ensure she was alert before administration of her methadone and SROM that day. They ended up holding her dose on day 4 and starting the 30mg on day 5.
- She missed day 6, dosed days 7 and 8 and missed day 9 because she didn't have bus fare.
- Today is Day 10. She is alert. She is asking to increase her methadone and kadian dose both as she is still in withdrawal.
- Can you increase her dose?

Maria

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day10
20mg	20mg	20mg	Held	30mg	Miss	30mg	30mg	Miss	?

Would it matter what her UDS showed?
Would you increase both her methadone and her kadian?
Are there any other considerations? What about her drinking?
When would you want to see her back?

Wrap-Up

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