Inner City Medicine - Hot Topics Review:

Managing Opiate Use Disorder – Sustained Release Oral Morphine

VCH AND BCCfE
Sept 30 2019
Dr. David Tu, MD, CCFP
Urban Indigenous Health & Healing Cooperative

Faculty/Presenter Disclosure

- **Faculty :Dr. David Tu**
- **Relationships with financial sponsors:**

  - **Industry**: In the past 2 years I have been a member of the Scientific advisory board for: **Gilead, ViiV**

  - **Non-Profit:** I am Board Treasurer, Operations Lead, and Family Physician with the Urban Indigenous Health & Healing Cooperative

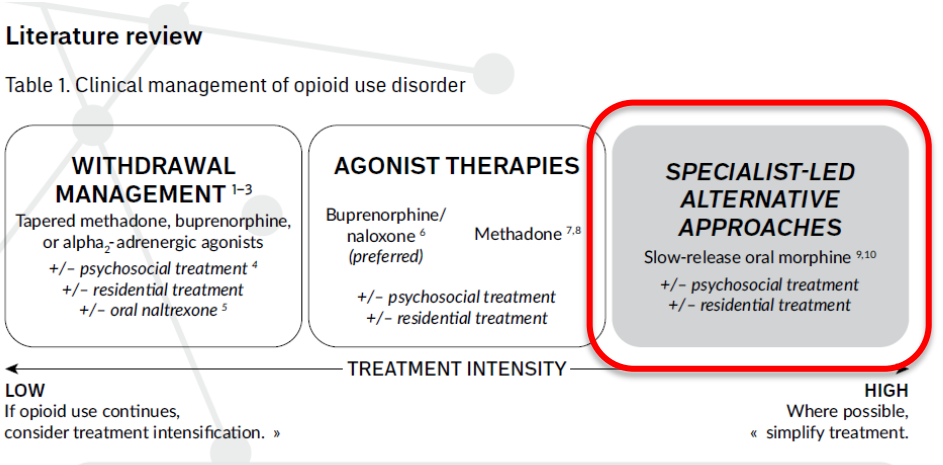
Mitigating Potential Bias

I agree to use generic names of medications in this presentation

I agree to identify when discussing an off label use of a medication

Sustained Release Oral Morphine(SROM):

- SROM refers to the once-daily 24-hour formulation of the extended-release morphine sulfate capsules (brand name Kadian®)



Learning Objectives–

By the end of this presentation participants will…

- Be able to apply a “framework” of opiate use disorder treatment considerations relevant to SROM.

Warning: This is an off label use of SROM

- Have considered some challenging clinical circumstances relevant to SROM.

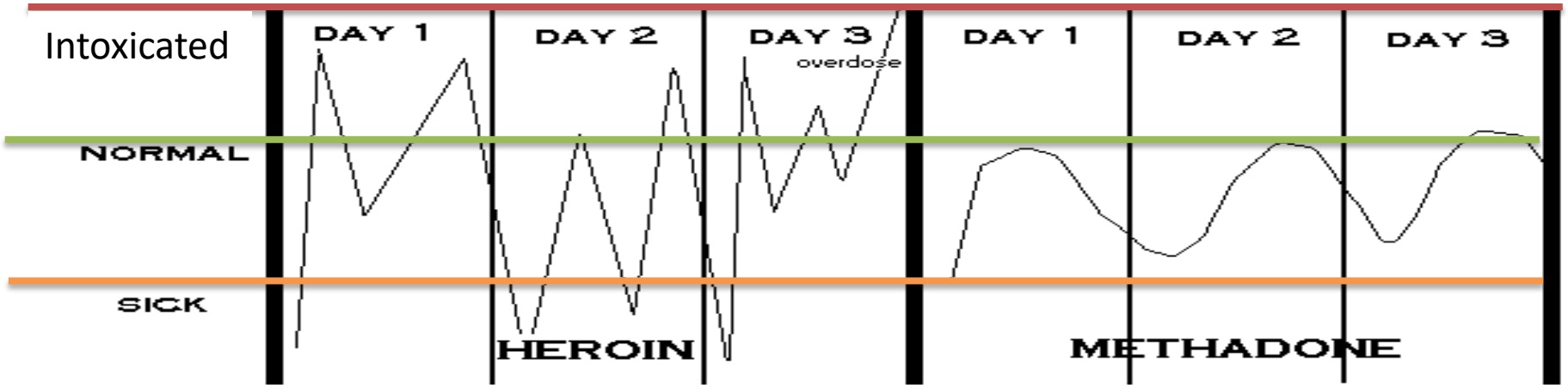
OAT Rx Considerations:

- Effectiveness:
  - Opiate use stability (Cravings/WD)
  - Cessation of non-prescription opiate Use
  - Social stability (income / crime / housing / connection to family & friends /"wellness")
  - Retention in care*
  - Survival
- Patient Factors/ Preference
- Provider Factors / Preference
- Adverse Events / Safety
- Drug Interactions
- Induction & Administration Issues
- Misuse / Diversion Risk

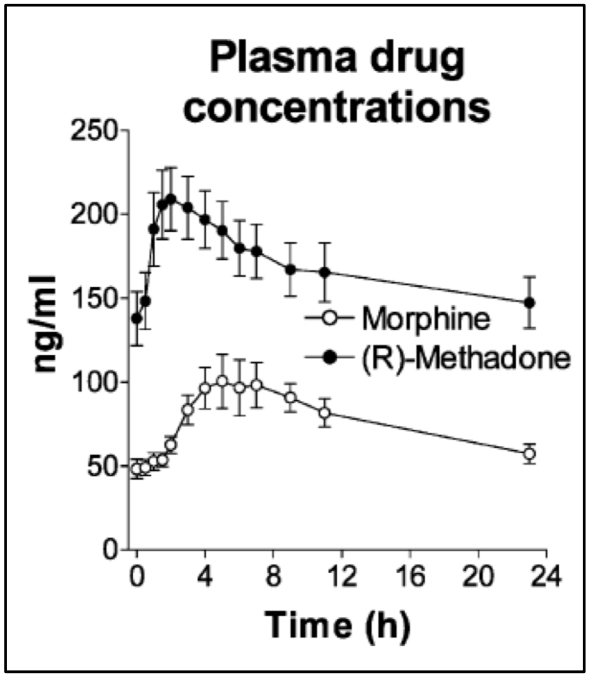
OAT Rx Considerations:

OAT Rx	Effective-ness	Patient Factors	Provider Factors	Safety	Drug Interactions	Administration	Misuse / Diversion Risk
Methadone							
Bupranorphine/ Naloxone (Suboxone®)							
SROM (Kadian®)							

SROM: Pharmacology



- Morphine is a full opioid agonist and is relatively selective for the mu-opioid receptor [8]
- SROM is released over 24 hours [8]
- Peak plasma levels are achieved in aprox 10 hours [8]
- The elimination half-life of SROM following a single dose is approximately 11 to 13 hours due to the delayed absorption of the pellets [8]
- Once absorption is complete, the plasma elimination half-life is the same as immediate-release morphine (2 to 4 hours) [8]



Case: CK(2017)

- 52 y.o. single Indigenous (Cree) female; moved from Winnipeg in 1992; living alone in DTES supported housing; & receiving disability benefits.

- 12 year history of severe opiate use disorder (since age 40); multiple recent overdose events; has had multiple attempts with methadone for OAT, and unsuccessful attempt with bupranorphine/naloxone.

- Discharged 3 wks ago on Methadone 80 mg (post sternal osteomyelitis rx), but discontinued in community; currently using $50/d of illicit opiates by injection (motivation for use = withdrawal rx / pain rx)

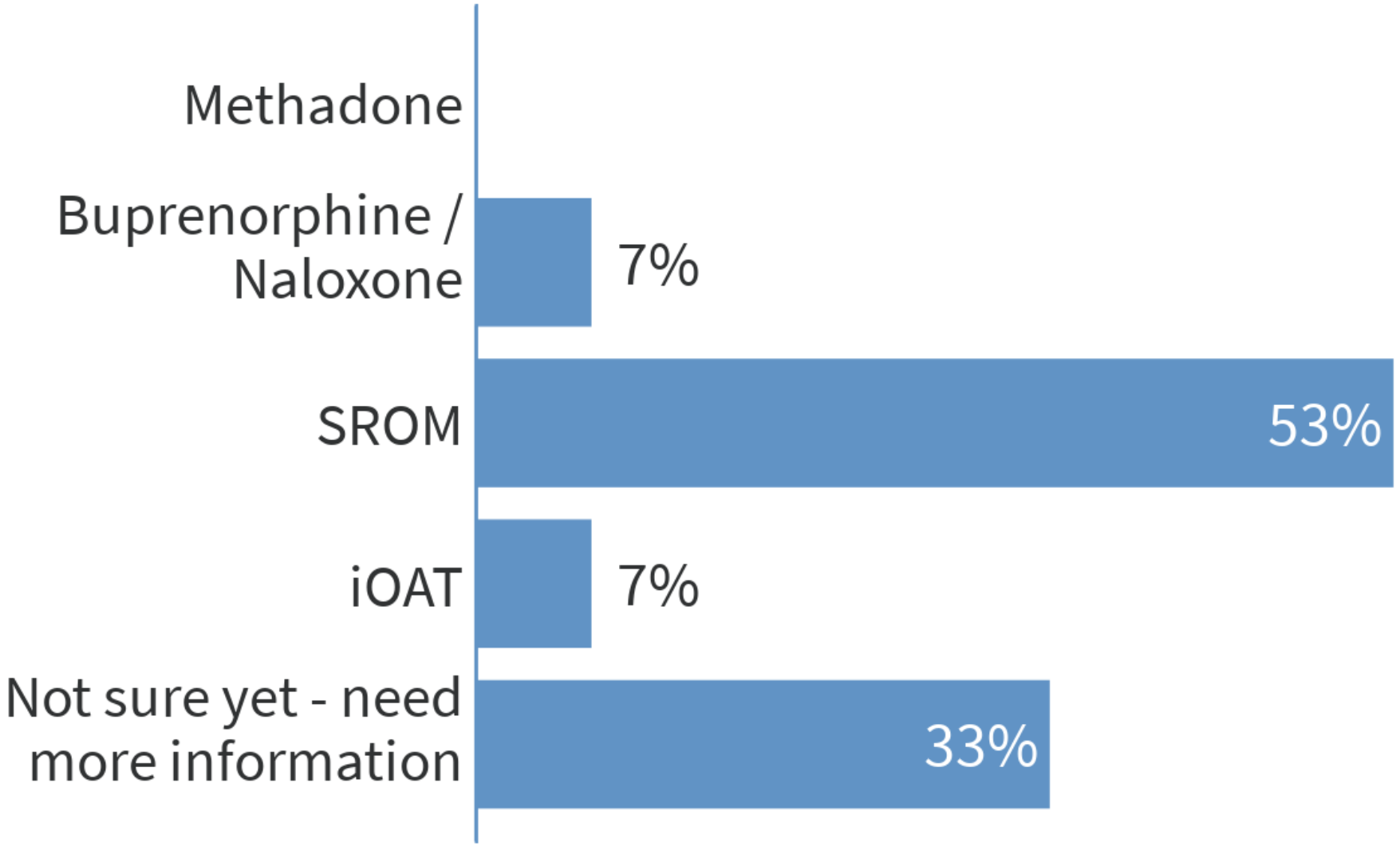
- PMHx: , L-spine epidural abscess (2007), HCV infection with spontaneous cure (2008), MV Endocarditis (2012) , C5-6 facet septic arthritis & epidural abscess (2013), Chronic LBP / OA.

- Psych Hx: Severe AUD from age 20-40 – remission; Moderate SUD (CM) – contemplative; ? underlying anxiety disorder/ PTSD

- Medications: Fluconazole (x6 months) ; methtrimeprazine prn

- Presenting to clinic with new injection related soft tissue infection, and open to re-initiation of OAT

What form of OAT would you recommend to CK?



SROM: Effectiveness

- Opiate Use Stability (Cravings/WD):
  - " Switch Studies"-- Cravings:
    - 18 pts/single arm crossover design/ VAS rating - - Superior to Methadone at 4 wks on stable dose [1]
    - 200 pts/two way crossover design/ VAS rating - Superior to Methadone at 25 wks [4]
    - 157 pts/RCT two way crossover design/VAS rating – Superior to Methadone at 22 wks [6]
  - "Salvage Study"-- Withdrawal & Craving:
    - "Salvage" – 29 pts/single arm crossover design/SOWS score/VAS rating– Superior to Methadone at 4 wks [2]
- Social Stability (Income / Crime / Housing / Connection to Family & Friends/ "Wellness"):
  - Depressive Symptoms : Meta Analysis – 3 RCT – superior to methadone [3]
  - Mental Health Symptoms: RCT/157 patients to way crossover design/ SCL 27 – superior to methadone [7]
- Cessation of Illicit Opiate Use (-ve UDS)
  - "Switch" -157 RCT –two way crossover - Similar to Methadone (80% neg UDS for heroin) [5]
- Retention in care:
  - "Meta Analysis" – 3 RCT – similar retention to methadone [3]
  - "Treatment Satisfaction" - RCT –157 pts -two way crossover – superior to methadone [7]
- Survival
  - Overdose Risk ???
  - Mortality: no difference to methadone at 22 wks [5]

SROM Patient Factors:

- Past Rx Experience:
  - Adverse events;
  - Effectiveness;
  - Reasons for discontinuation
- Current Social Context:
  - Housing / Income / Social Connection / Supports
- Preference:
  - Willingness for Methadone or BN
  - Willingness for SROM
- Treatment Readiness:
  - Importance
  - Confidence

CK Con'd:

- Past Experience:
  - Did not find methadone beneficial for her back pain nor effective for control of cravings
  - Did not find BN effective at controlling withdrawal / cravings / pain
- Current Context:
  - Fair social stability / supports
- Preferences:
  - Does not want to try methadone or BN again
  - Willing to try SROM
- Readiness:
  - 8/10 importance to stop IDU (recent overdose events)
  - 8/10 confidence to achieve "stability"

SROM Provider Factors:

- Past Experience:
  - SROM knowledge / clinical experiences
- Current Context:
  - Urgency
  - Resources
- Preferences:

CK Con'd

- Provider Experience:
  - comfortable and experienced with SROM from chronic pain / palliative care context
- Context:
  - Urgent need for stability to prevent further morbidity or loss of life
- Preference:
  - Need to try something new as previous attempts with Methadone & BN were not effective

ADVERSE REACTIONS

- **Adverse Effects (Clinical Trials)**:
  - open-label, 4-week safety study, 1418 patients ages 18 to 85 with chronic, non-malignant pain[8]
  - Most common: constipation (12%), nausea (9%), and somnolence (3%) [8]
  - Less common (<3%) : vomiting, pruritus, dizziness, sedation, dry mouth, headache, fatigue, and rash [8]
  - Similar rate of Adverse effects between Methadone & SROM[5]
- **Post-Marketing Experience** [8]
  - Serotonin syndrome
  - Adrenal insufficiency
  - Anaphylaxis
  - Androgen deficiency

DRUG INTERACTIONS [8]

- Alcohol
- Benzodiazepines and Other Central Nervous System (CNS) Depressants (sedation /resp depression)
- Serotonergic Drugs (serotonin syndrome)
- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics (withdrawal)
- Muscle Relaxants (resp depression)
- Cimetidine (resp depression)
- Diuretics (reduced effect of diuretics)
- Anticholinergic Drugs (urinary retention / constipation)
- PGP-Inhibitors (increases serum morphine levels x2)

Administration:

- **Dosage Forms (Canada)**: 10 mg, 20 mg, 50 mg, 100 mg Capsules[9]

- **Dosing Adjustments:** every 1 to 2 days (as steady-state plasma concentrations within 24 to 36 hours) [8]

- **Opiate Equivalency**: between 8:1 to 5:1 ratio to methadone [1]

- **Dose Ingestion:** Capsules must be taken whole or "pellets" may be sprinkled over applesauce and then swallowed. (Crushing, chewing, or dissolving the pellets will result in uncontrolled delivery of morphine) [8]

Diversion Risk / Misuse:

- If sprinkled pellets in applesauce and witnessed ingestion with mouth rinse post ingestion – diversion risk is low.
- Real world: most pharmacies do not use applesauce; some use water; some just put pellets in a cup. ? Diversion risk still likely low.
- Without sprinkling – diversion is very feasible.
- “Cooking” & injecting SROM pellets is possible but technically difficult

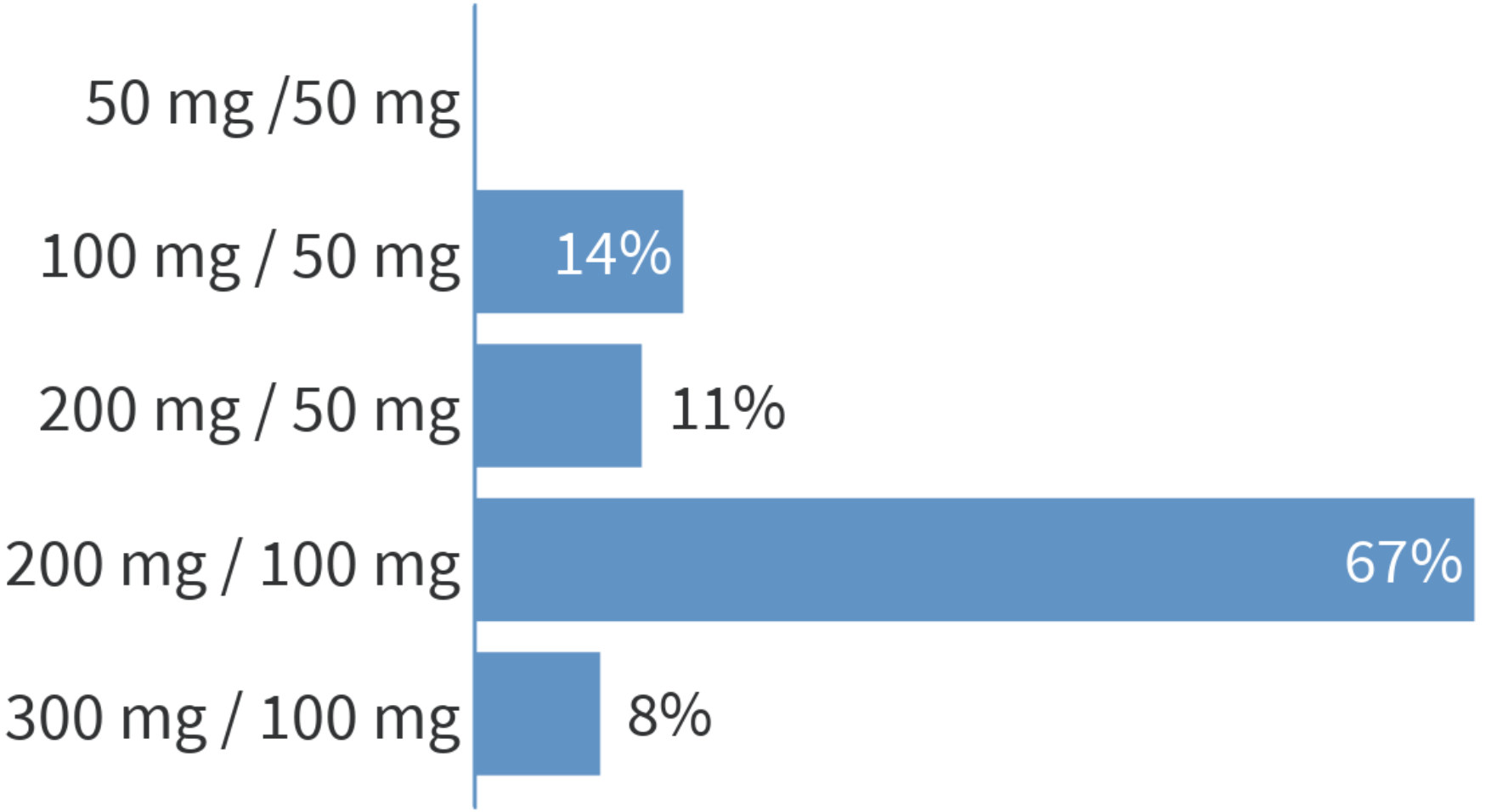
OAT Rx Considerations:

OAT Rx	Effective-ness	Patient Factors	Provider	Safety	Drug Interactions	Administration	Misuse / Diversion Risk
Methadone							
Bupranorphine/Naloxone (Suboxone*)							
SROM (Kadian*)	Similar to Methadone ↑Stability ↑ MH	Pain Rx MH Rx		Similar to Methadone Histamine Reactions & SS; no↑ QTc	Similar to Methadone Cimetidine Diuretics PGP I	More rapid titrations than methadone	Low with DWI Sprinkled Pellets

CK Con’d

- After reviewing the effectiveness and side effect profile, CK agrees to a trial of SROM with the shared goal of opiate stability & adequate pain control.

What dose would you start with and at what dose would you up titrate?



CK Con'd:

- Started at 250 mg (equivalent to 30 mg methadone at 8:1 ratio)
- Up titrated q 1-2 d at 50-100 mg
- CK achieved opiate stability at 500 mg SROM once daily sprinkled and adequate sternal & back pain control.

CK Con'd:

- Completed 6 month rx with fluconazole – CRP remained low
- 2018: Develops worsening bil hip pain, neck pain, and neuropathic pain and weakness in arms and legs – mostly at night. Has been "self-medicating" with inhaled NP opiates (fentanyl) - $40/d.
- States: SROM is no longer working for my pain.
- Requesting change to something else.

CK Con'd:

- Context:
  - socially stable
  - Highly motivated for abstinence to avoid overdose or further infections
  - Therapeutic relationship x 6 years -- I trust her

- What would you do next regarding OAT?

M-Eslon® (12 hr SR)

- M-Eslon®: 10 mg, 15 mg, 30 mg, 60 mg, 100 mg, 200 mg [8]
- Dosing: BID or TID [8]
- 4 hr to peak serum levels vs 10 hrs with Kadian® [8]
- CK established adequate pain control with 300 mg BID; PM dose daily dispensed.

CK Con'd:

- Not using illicit opiates (by hx; neg UDS for fentanyl x 1) for 4 wks

- Does not want to continue sprinkles … she has poor dentitian and pellets getting stuck in her teeth. PM Dose is not sprinkled.

- What do you do?

UIHHC Sprinkles Draft Policy:

- "To reduce the risk of diversion or misuse of SROM for OAT, for people initiating and re-initiating treatment, doses of SROM will be sprinkled and witnessed in pharmacy; sprinkles will continue until "stability" with respect to NP opiate use is achieved for a (?) 2 month period."

CK Con’d

- Sprinkles were discontinued, and remained stable for several months.
- Worsened hip pain – became wheel chair bound – began “self medicating” again with inhaled NP fentanyl
- Admitted to hosp in early 2019 with dx with R hip septic arthritis and C-45 central stenosis; recently discharged on 700 mg MESLON® bid

Questions?

References

1. Mitchell TB, White JM, Somogyi AA, Bochner F. Slow-release oral morphine versus methadone: a crossover comparison of patient outcomes and acceptability as maintenance pharmacotherapies for opioid dependence. Addiction. 2004;

2. Kastelic A, Dubajic G, Strbad E. Slow-release oral morphine for maintenance treatment of opioid addicts intolerant to methadone or with inadequate withdrawal suppression. Addiction. 2008;103(11):1837–1846.

3. Ferri M, Minozzi S, Bo A, Amato L. Slow-release oral morphine as maintenance therapy for opioid dependence. Cochrane Database Syst Rev. 2013(6):CD009879.

4. Hammig R, Kohler W, Bonorden-Kleij K, et al. Safety and tolerability of slow-release oral morphine versus methadone in the treatment of opioid dependence. J Subst Abuse Treat. 2014;47(4):275–281.

5. Beck T, Haasen C, Verthein U, et al. Maintenance treatment for opioid dependence with slow-release oral morphine: a randomized cross-over, non-inferiority study versus methadone. *Addiction* 2014;109(4):617-626.

6. Falcato L, Beck T, Reimer J, Verthein U. Self-Reported Cravings for Heroin and Cocaine During Maintenance Treatment With Slow-Release Oral Morphine Compared With Methadone A Randomized, Crossover Clinical Trial. J Clin Psychopharmacol. 2015;35(2):150–157.

7. .Verthein U, Beck T, Haasen C, Reimer J. Mental Symptoms and Drug Use in Maintenance Treatment with Slow-Release Oral Morphine Compared to Methadone: Results of a Randomized Crossover Study. Eur Addict Res. 2015;21(2):97–104.

8. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020616s061s062lbl.pdf#page=34

9. https://www.uptodate.com/contents/morphine-drug-information?search=kadian&source=panel_search_result&selectedTitle=1~148&usage_type=panel&kp_tab=drug_general&display_rank=1