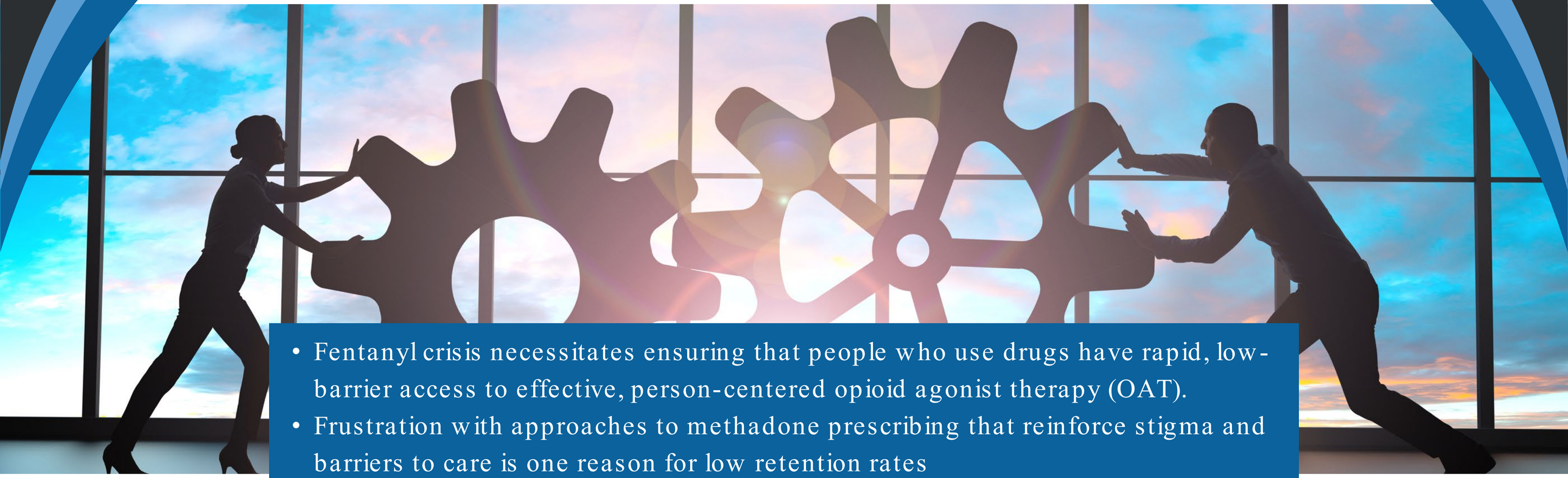
RECOMMENDATIONS FOR USE OF SLOW-RELEASE ORAL MORPHINE AS OPIOID AGONIST THERAPY

Jason Rodgers, Ashley Smoke & Suzanne Turner

METAPHI
MENTORING, EDUCATION, AND CLINICAL TOOLS FOR ADDICTION
PARTNERS IN HEALTH INTEGRATION

Urgent Need for Expanded Treatment Options



- Fentanyl crisis necessitates ensuring that people who use drugs have rapid, low-barrier access to effective, person-centered opioid agonist therapy (OAT).
- Frustration with approaches to methadone prescribing that reinforce stigma and barriers to care is one reason for low retention rates

FAILURE TO MEET PATIENTS' SELF-IDENTIFIED NEEDS CONTRIBUTES TO LOW TREATMENT RETENTION RATES, WHICH IN TURN ARE ASSOCIATED WITH HIGH RISKS OF RELAPSE AND DEATH

The Historical Approach

Withdrawal Management[1-3]	Agonist Therapies		Specialist-Led Alternative Approaches
Tapered methadone, buprenorphine alpha$_2$-adrenergic agonists +/- psychosocial treatment[4] +/- residential treatment +/- oral naltrexone[5]	Buprenorphine/ naloxone[6] *(preferred)*	Methadone[7, 8]	Slow-release oral morphine [9, 10] +/- psychosocial treatment[4] +/- residential treatment
	+/- psychosocial treatment[4] +/- residential treatment		

LOW ***TREATMENT INTENSITY*** **HIGH**

If opioid use continues, consider treatment intensification. >>

<<<<<<< Where possible, simplify treatment.

The Guidelines

- CRISM (2018) National Guideline for the Clinical Management of Opioid Use Disorder
  - Buprenorphine is first line >> Methadone
- CAMH (2021) Synthesis of Canadian Guidelines for Treating Opioid Use Disorder
  - Buprenorphine > Methadone >>>> SROM
- Meta:PHI (2021) Methadone Treatment for People who use Fentanyl
  - Buprenorphine = Methadone
- BC (2022) Opioid Use Disorder Practice Update
  - Buprenorphine = Methadone = SROM

The Patient Perspective

“When I made the decision to recover from years of opiate use, the option of methadone was very stigmatizing and time-consuming. I didn't want to wait at the pharmacy every morning just so that I could function. My family doctor and I came up with a plan to wean off opiates with Kadian. It was tough in the beginning, but after a few days we were able to get to the correct dose and I started to feel normal again. After 8 months of titrating my dosages down slowly, I was able to come off Kadian. Although therapy was also a big component of my recovery, there is no way I could have gotten to my appointments without Kadian. Giving people who suffer from substance use disorder more options in their recovery empowers them to make better decisions and to be a part of the way forward in the decision-making process.” –Jason

The Patient Perspective

“I was on methadone for 7 years, and while very high doses twice a day took care of my withdrawal and helped me stay off other opioids, it never took care of the cravings, and I was very depressed, unmotivated, and still in extreme physical pain – the reason for the opioids in the first place. After a relapse to fentanyl (the only available option), I found someone willing to prescribe Kadian alongside methadone. The addition of Kadian provided the extra relief I needed for withdrawal. It eventually eliminated my opioid cravings, and it has also helped with my depression and my ulcerative colitis. I have attempted multiple medical-assisted opioid treatments, but this is the most successful treatment for me. By choosing my own path, I was able to take ownership over my well-being and I am the healthiest I have ever been.” –Ashley

Methodology

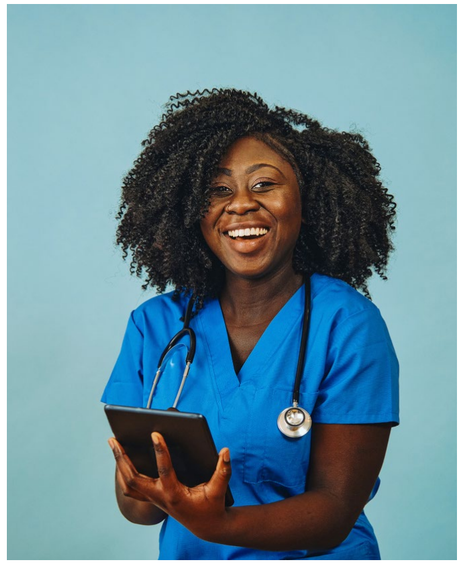
- An electronic search was conducted on PubMed and Google Scholar using subject heading search terms and keywords associated with the concepts of morphine, slow release oral morphine, Kadian®, SROM, opioid agonist therapy, and opioid substitution treatment.
- Key words and headings were additionally derived by reviewing the titles and abstracts of identified articles and systematic reviews.
- Grey literature including provincial and national guidelines for opioid agonist therapy and medication safety were included.
- Articles included were limited to studies and reports published since 1996 in English.

SROM Guideline Team

2 People with Lived/Living Experience

3 Physicians

1 Pharmacist



1 Nurse Practitioner

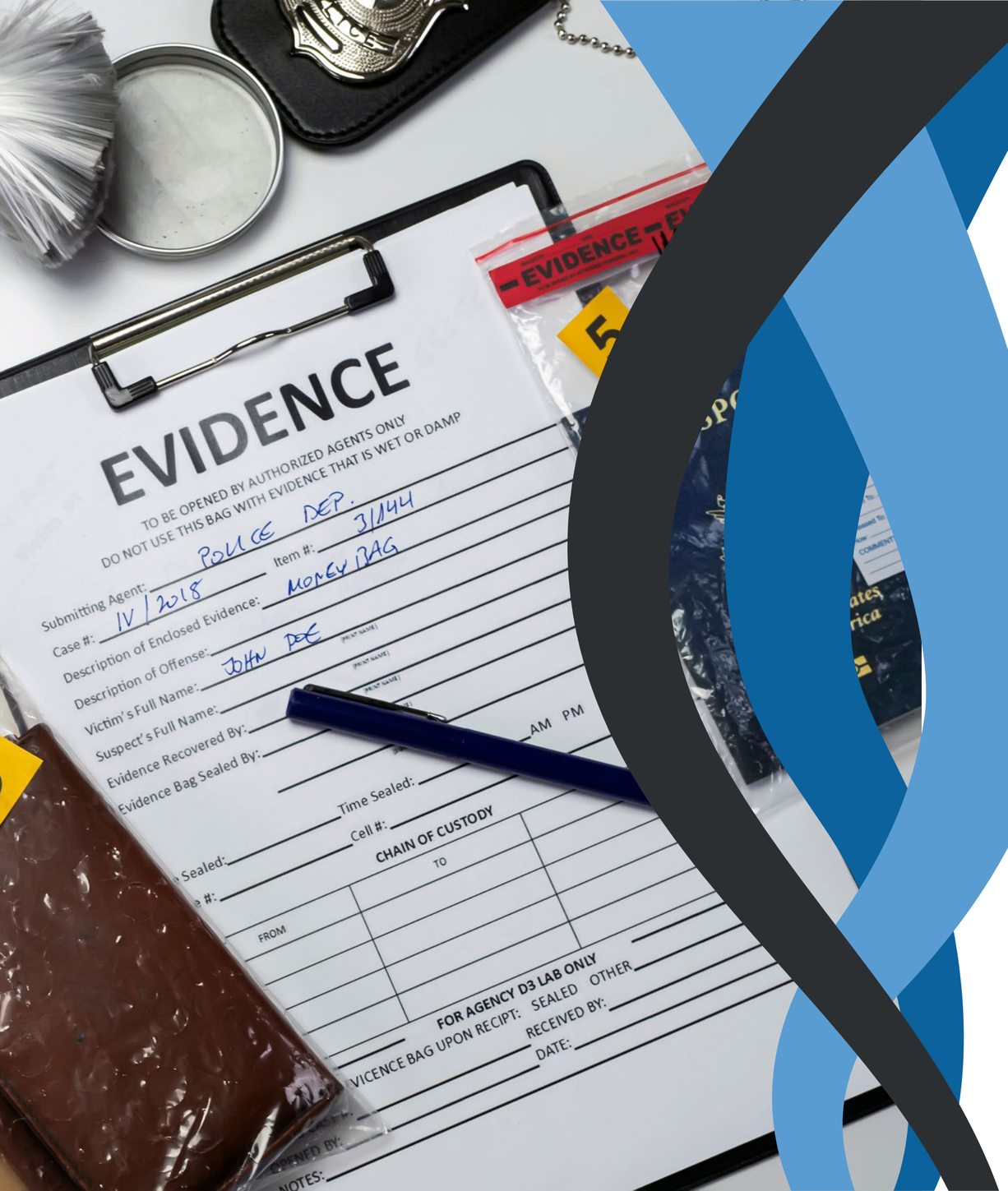
- The group reviewed the formal literature and considered the experiences and perspectives of the authors around each sub-theme with the support of a moderator
- Through an iterative process of discussion and refinement, the group generated the consensus-based guidance document
- The resulting document is not based on a GRADE framework due to the current lack of high-quality evidence.
- Expert opinion / Lived/ Living experience has high prominence

Story About
Ted & SROM

- 36 year old
- Lives in an encampment
- DOC: fentanyl, smoked, mixed with meth
- Treatment experienced:
  - methadone (> 120 mg)
  - buprenorphine/naloxone (> 32mg)
  - ER-buprenorphine (injectable)
- Coming to RAAM asking for SROM

More About Ted & SROM

- Had unbearable sweating on methadone
- Felt like needed higher dose but was told couldn’t go above 120 mg
  - “something about my heart”
- Felt like bup/nlx and sublocade made him use more to overcome the effect
- Goal: reduce use so he can prevent overdose



Evidence for SROM as OAT

- Five systematic reviews of SROM as OAT over 10 years
- Very few high-quality studies
- Limitations:
  - weakness of most study designs (crossover studies, small sample sizes, and short duration
  - very limited number of components amenable to meta-analysis

Aspects of SROM Care

Retention

- Similar to Methadone and Buprenorphine based on Cochrane Review (2013)
- 2 Meta-analysis SROM = methadone i
- Prospective study : 71% SROM vs 47% methadone vs. 46% buprenorphine
- 60% SROM when voluntarily switched from M/Bup

Substance Use

- 2 meta-analysis: SROM vs Methadone - no difference in heroin or other substances
- Voluntary switch from M/Bup significant reduction or 50% reduction in another study

Cravings

- Prospective study and two cross over studies (involving methadone) found a reduction in cravings

Satisfaction

- Higher in open-label cross over studies with methadone
- Report feeling more “normal”

- 3 studies showed improved anxiety, depression and MH vs Methadone
- No studies MH + Bup

Recommendation 1

SROM be considered as an OAT option alongside buprenorphine and methadone

No expert / additional consultation needed

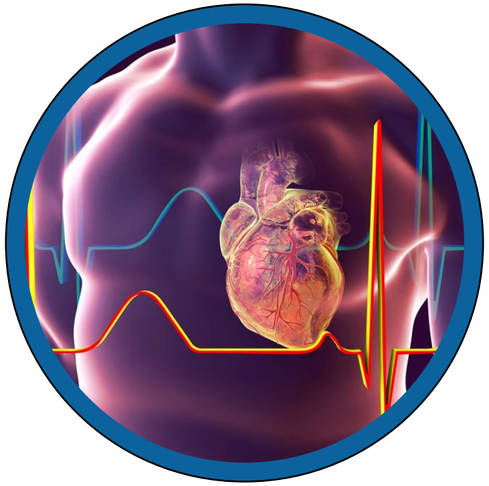
What About Safety?

Side Effects

- Expected to have more side effects compared to buprenorphine (full-agonist)
- Palliative patients, more side effects methadone > morphine
- No different in cross-over

Drug Interactions

- Limited interactions compared to methadone
- Interactions include:
- Some benzos
- Some TCAs
- Some CCBs (nifedipine)



Qt Prolongation

- Limited Qt Prolongation
- Limited risk of Torsades de Pointe

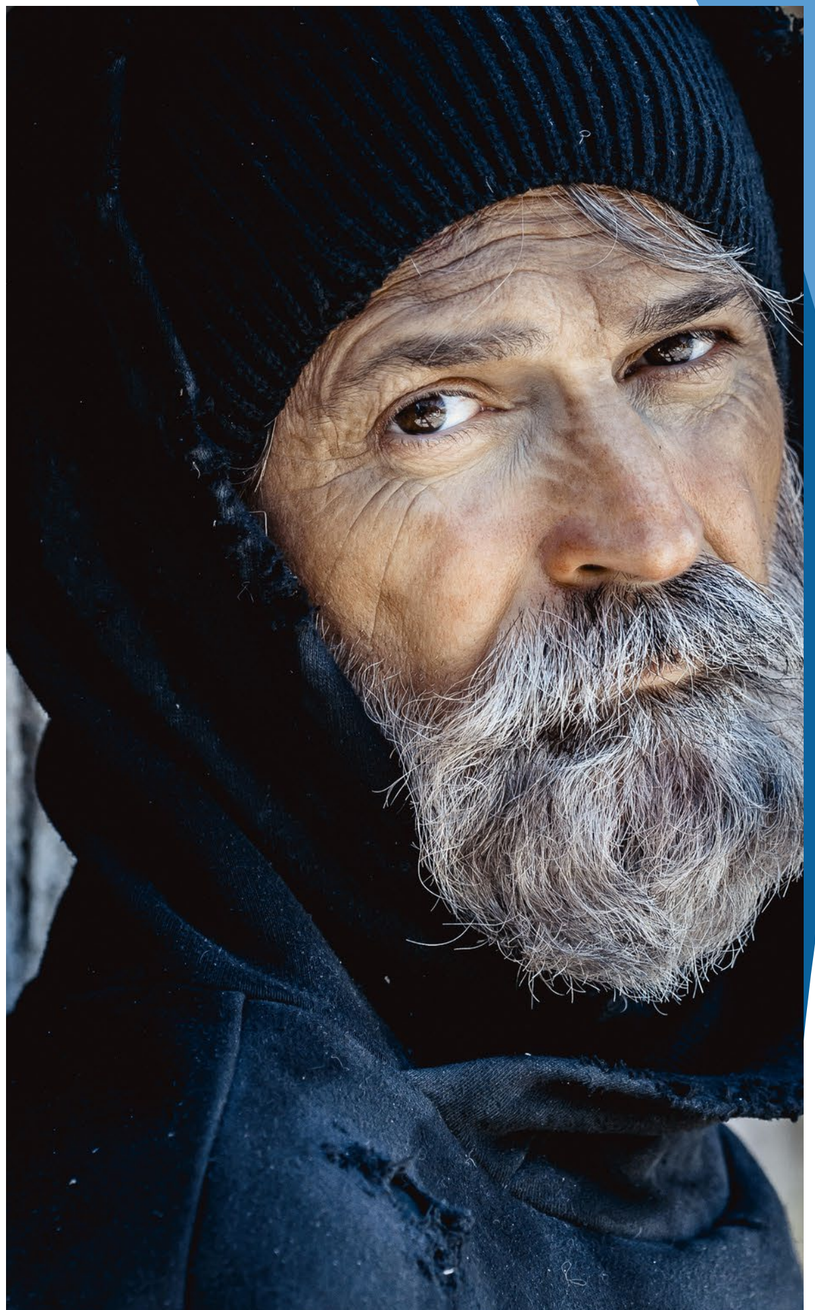
Recommendation2

Consider in specific populations:

- Severe OUD / high risk opioid use
- Unacceptable side effects on other OAT
- Ongoing cravings or w/d with other OAT
- High risk for prolonged QT or TdP

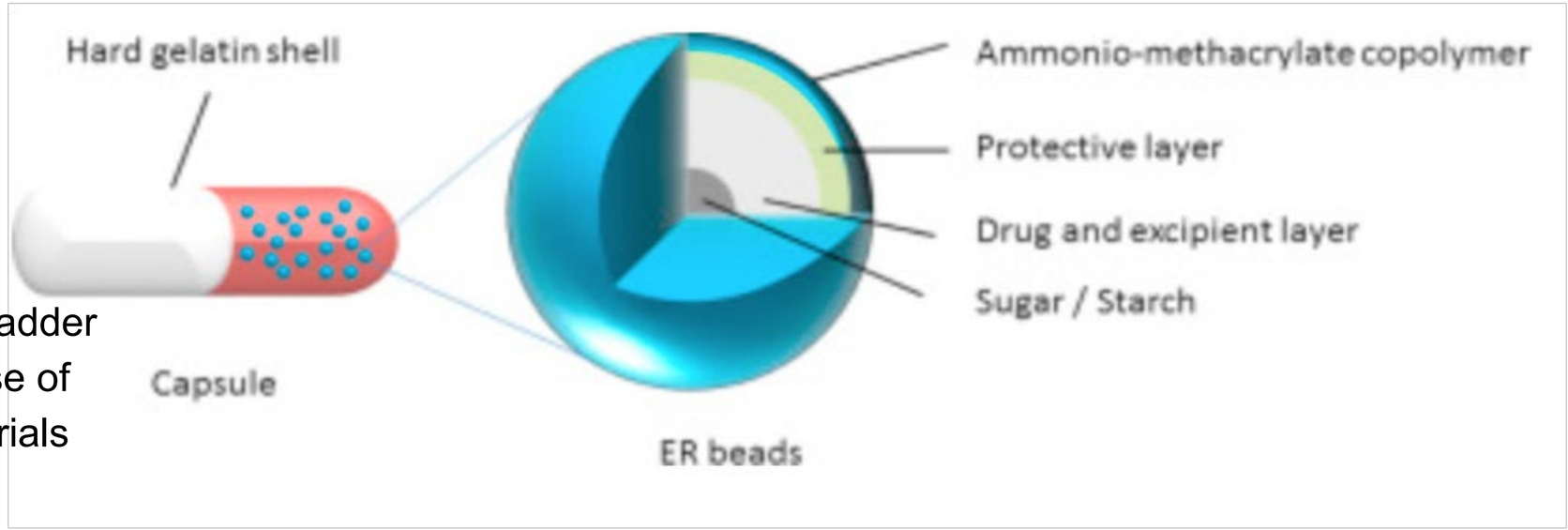
More About Ted & SROM

- Ted wants to get to a “good” dose quickly and wants to know what his starting dose will be?
- PMH:
  - Untreated HepC, no evidence of cirrhosis
  - ?Hx of Prolonged Qtc on methadone
  - No surgeries



SROM: Formulations

Martin C, De Baerdemaeker A, Poelaert J, Madder A, Hoogenboom R, Ballet R. Controlled-release of opioids for improved pain management. Materials Today. 19(9): 2016. 495-502.



- Generic: Morphine Sulphate Sustained Release Capsules; Trade name: Kadian®
- One type of beads: contains IR and SR morphine
- Gelatin capsule dissolves in GI fluid
- Insoluble ethyl-cellulose layer with two pore forming agents
- PEG (one of the pore-forming agents) releases IR morphine in the stomach (acidic pH)
- Ethyl acrylate methacrylic acid co-polymer breaks down in the small/large bowel at higher pH
  - releasing the SR morphine formulation
- Once daily, 24-hour formulation

SROM: Pharmacodynamics

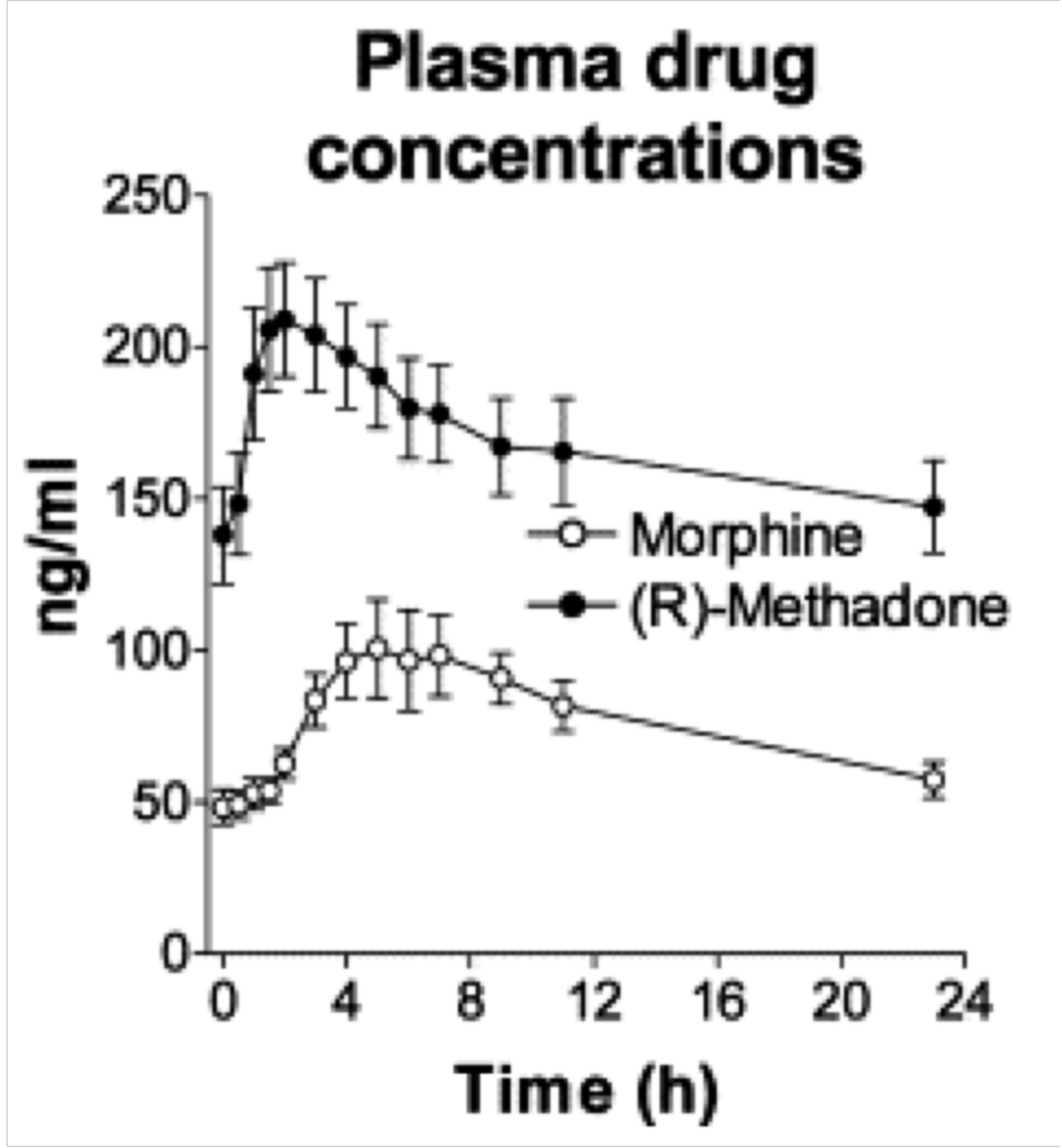
Indices of opioid effects during one 24 h inter-dosing interval for methadone and SROM maintenance (n=14). Plasma concentrations have been normalized to 70-mg racemic methadone and 300-mg morphine sulphate.

Peak plasma levels: 8.5-10 hours post dose

Elimination half life: 11-13 hours post dose

Steady-state: 48 hours post initial dose

Ceiling effect: None



Mitchell TB, White JM, Somogyi AA, Bochner F. Comparative pharmacodynamics and pharmacokinetics of methadone and slow-release oral morphine for maintenance treatment of opioid dependence. Drug and Alcohol Dependence. 2003. 72 (1): 85-94.

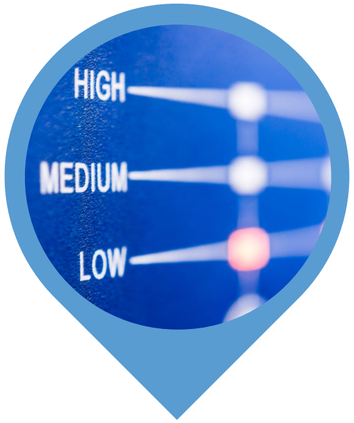
SROM Absolute Contraindications

- Hypersensitivity to morphine sulfate or any of the non-medicinal ingredients
- Acute or severe respiratory depression
- Asthma with severe bronchospasm
- Severe COPD
- GI obstruction, including ileus
- Use of a monoamine oxidase inhibitor within the last fourteen days
- Chronic kidney disease (GFR <50)

SROM Relative Contraindications

- Gastrointestinal issues that affect gastric emptying
  - obstruction, diarrhea, abnormal gut anatomy
- GFR between 50-90.
  - Renal function can be acutely reduced (e.g. by dehydration or medications), thereby putting patients at risk of M6G toxicity.
- Caution in people who drink alcohol.
  - Co-ingestion of alcohol and SROM morphine can cause a rapid increase in opioid plasma concentrations;
- Hepatic dysfunction.
- Higher risk for opioid toxicity: older age, COPD, sleep apnea, & sedatives

Starting Doses: Monotherapy



Low Tolerance

- 30 - 50 mg
- Low tolerance opioids
- Intermittent exposure
- High risk of toxicity

Mod Tolerance

- 100 - 150 mg
- Fentanyl tolerance
- Intermittent exposure
- Risk of toxicity (benzodiazepines)

High Tolerance

- 200 - 400 mg
- High Fentanyl tolerance
- Regular Exposure
- No toxicity risks

SROM Initiation & Titration

- The guidance in this document regarding dose initiation and titration is based on:
  - clinical experience and expert clinical consensus
  - refers specifically to the 24-hour once-daily formulation of slow-release oral morphine.
- Individual factors including opioid tolerance, concurrent substance use, medications and other medical conditions.

CONSIDERATIONS FOR SROM STARTING DOSES

Recent clinical experinence higher starting doses of methadone

30-50 mg of methadone

Accepted conversions of methadone to SROM (1:4 to 1:8

Can use 1:6 conversion

For example = 50 mg methadone x 6

Starting dose of 300 mg

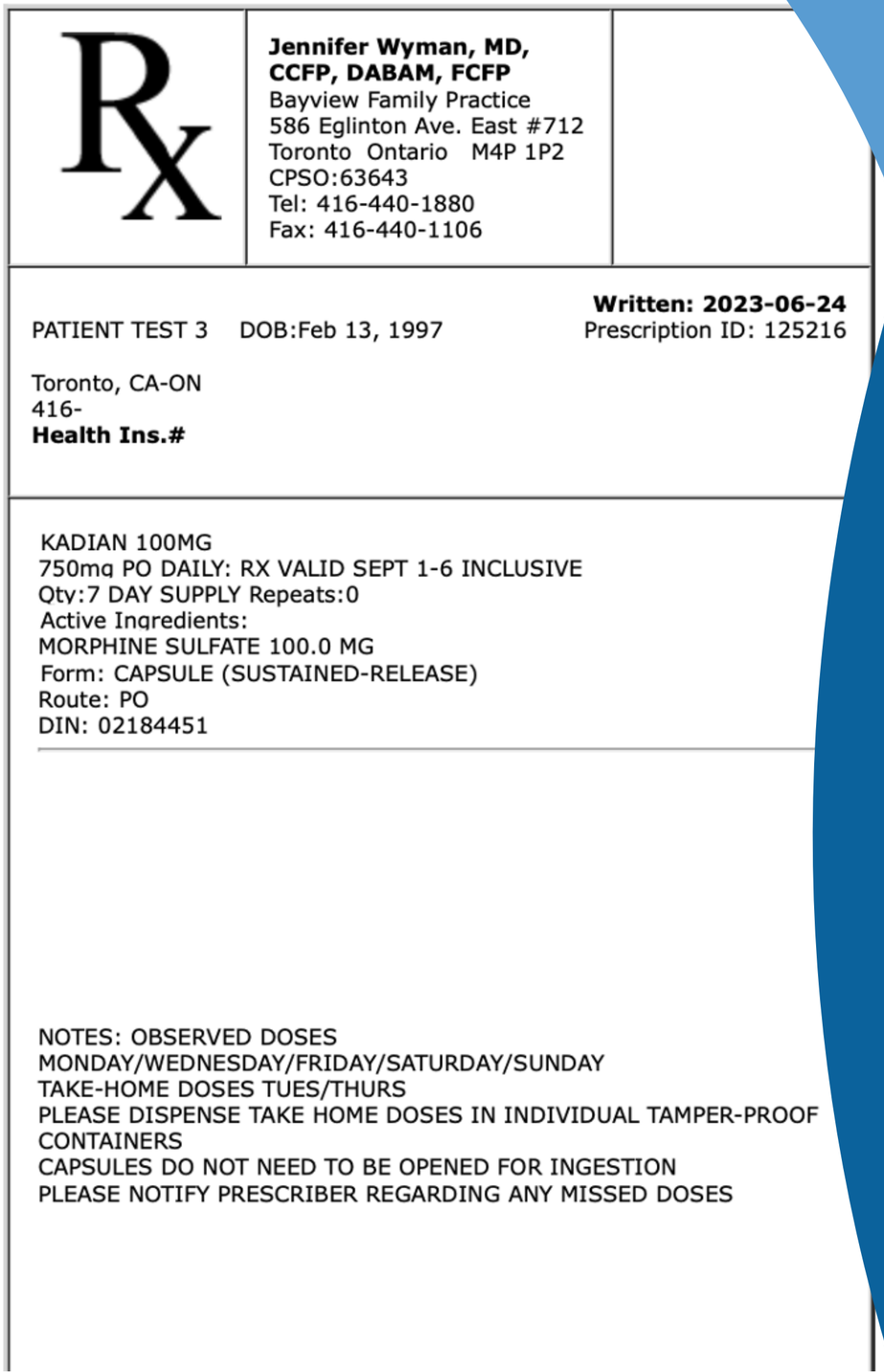
Other clinical experience: 30 mg of methadone + 200 mg of SROM

Starting dose of 380 mg

SROM Titration

Opioid tolerance	Starting dose	Titration
Low tolerance or high risk for toxicity	30–50 mg	50 mg every 48 hours
Moderate tolerance	100–150 mg	50–100 mg every 48 hours
High tolerance	200–400 mg	100 mg daily OR 200 mg every 48 hours to 800 mg Thereafter 50–200 mg every 48 hours

- No maximum daily dose
- Literature maximum dose: 1200 mg
- Clinical experience maximum dose: > 2000 mg
- Goal: minimal withdrawal / without sedation / minimal side effects



Rx

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Bayview Family Practice
586 Eglinton Ave. East #712
Toronto Ontario M4P 1P2
CPSO:63643
Tel: 416-440-1880
Fax: 416-440-1106

Written: 2023-06-24
Prescription ID: 125216

PATIENT TEST 3 DOB:Feb 13, 1997

Toronto, CA-ON
416-
Health Ins.#

KADIAN 100MG
750mg PO DAILY: RX VALID SEPT 1-6 INCLUSIVE
Qty:7 DAY SUPPLY Repeats:0
Active Ingredients:
MORPHINE SULFATE 100.0 MG
Form: CAPSULE (SUSTAINED-RELEASE)
Route: PO
DIN: 02184451

NOTES: OBSERVED DOSES
MONDAY/WEDNESDAY/FRIDAY/SATURDAY/SUNDAY
TAKE-HOME DOSES TUES/THURS
PLEASE DISPENSE TAKE HOME DOSES IN INDIVIDUAL TAMPER-PROOF CONTAINERS
CAPSULES DO NOT NEED TO BE OPENED FOR INGESTION
PLEASE NOTIFY PRESCRIBER REGARDING ANY MISSED DOSES

SROM: Pharmacy Considerations

- The prescription should include wording that advises the pharmacist to use whatever combination of strengths are available to make the total daily dose
- Capsules do not need to be opened with pellets poured into a cup for observed dosing.
  - Opening of capsules creates a workflow issue for pharmacists
  - Opening many capsules into cups that may retain pellets during dosing due to static, obtaining yoghurt or apple sauce)
  - Barrier for people taking SROM (having to wait until the pharmacist has time, stigma of taking a medication in unique and obvious ways).
- We recommend that capsules be swallowed whole for observed doses, followed by a swallow of liquid

Recommendation 3

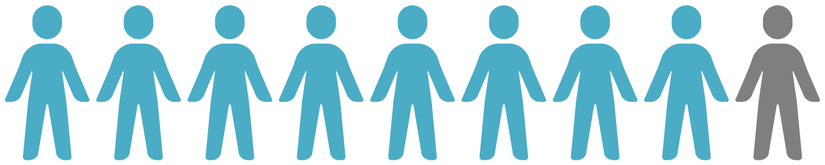
- SROM starting doses should be based on the individual's opioid tolerance and risk of toxicity.
- Can be as high as 200-400 mg for those with high tolerance
- No maximum daily dose

More About
Methadone & SROM

- Let’s say instead of starting SROM Ted wants to switch from methadone
- He’s been on 100 mg of methadone for many years and is unable to go up because of a prolonged Qt
- He doesn’t like the idea of being on methadone and SROM
- Goal: SROM Monotherapy

SROM CONVERSIONS

- No clear evidence for one approach over the other from the limited literature. T
- 2 studies: stop methadone and initiating SROM
  - An abrupt stop and start may result in higher rates of withdrawal while doses are being adjusted.
  - This approach may be more appropriate for a monitored setting where withdrawal can be managed with short-acting morphine.
- Individual circumstances such as medical stability, tolerance, experience with SROM, and opportunities for monitoring and reassessment should be considered.
- The usual final dose of SROM is between 1:6 and 1:8 of methadone to SROM.



METHOD 1: ABRUPT STOP & START

METHOD 2: CROSS TAPER

Cross Taper Transition

- Unpublished methadone and SROM simulation studies conducted by Mundipharma Limited informs our approach
- showed that overlapping methadone and SROM results in peak concentrations above the steady state peak concentrations for methadone alone.
- Their protocol: starting SROM at 25-30% of the anticipated final SROM dose (using a 1:6 ratio) along with 50% of the usual methadone dose and cross-tapering from there.

	Methadone	SROM
Day 0	100 mg	
Day 1	50 mg	150 mg
Day 2	30 mg	300 mg
Day 3	20 mg	400 mg
Day 4	0 mg	500 mg
Day 5		600 mg

Recommendation 4

- Cross-tapering may be more appropriate than an abrupt stop and start transition between OAT medications.
- The usual final dose of SROM is between 1:6 and 1:8 of methadone to SROM

More About
Ted & SROM

- Ted has been on SROM for 4 weeks
- He's current dose is 650 mg daily
- You get a call from the pharmacy
  - Ted is presenting after 3 missed doses of SROM; presenting day 4
- The pharmacist would like to know what you would like to do?

SROM Missed Doses

- Previous guidelines reduce the dose of SROM by 40% with two consecutive missed doses
- Based on short half life (8 hours) for SROM compared to 59 hours for methadone
- CLINICAL EXPERIENCE IN THOSE WITH UNREGULATED OPIOIDS HAVE ONGOING TOLERANCE
- Recommendations: in line with the META:PHI methadone for those use fentanyl

Days missed	Dose
Three (patient presents on Day Four)	Continue previous dose; no adjustment required
Four (patient presents on Day Five)	50% of previous dose or initiation dose (whichever is higher)
Five or more (patient presents on Day Six or later)	Re-start

For people on doses above 800mg morphine/day we recommend that doses generally be reduced by 40% after two consecutive missed doses, with room for consideration of individual tolerance and circumstances.

Recommendation 5

- Missed doses: No dose adjustment for three consecutive missed doses
- Reduction of 50% or to an initiation dose (whichever is higher) after four consecutive missed doses
- Doses > 800 mg/d, consider reducing dose by 40% after 2 missed consecutive doses

More About
Ted & SROM

- Ted has been on SROM for 3 months
- His current dose is 1200 mg / day
- He hasn’t missed a dose in 2 months
- Ted recently received ODSP and is now housed in a supportive mental health building
- He’s wondering if he can start to build carries?

Urine Drug Screening

BCSSU and Meta:PHI congruent with following:

Treatment stage	UDT frequency
Titration, stabilization, and building carries	Usually up to four times per month, typically in conjunction with an appointment
Long-term carries, six or more	Usually every one to two months, typically in conjunction with a clinical assessment (more frequently if clinically indicated) At the request of the person receiving methadone, if they wish to know what is in their sample
Maintenance of methadone for people not receiving or building carries	Monthly OR more or less frequently as clinically indicated, in conjunction with a clinical assessment

SROM: Urine Drug Screen Interpretation

Substance	Expected findings on mass spectrometry
Morphine	Morphine (very high) Hydromorphone (variable, proportionate to dose of morphine) Codeine (trace, i.e., <50 mg/mL)
Heroin	Heroin metabolite 6-acetylmorphine (6-MAM) Morphine (variably high) Codeine (5–10%) 6-acetyl codeine may be present as a contaminant (marker of street heroin
Hydromorphone	Hydromorphone Hydromorphone 3-glucuronide (hydromorphone metabolite)
Codeine	Codeine (high) Morphine (low)

SROM
Carry Criteria

- SROM for at least 4 weeks
- Able to store medication safely
- Stable mental health
- No missed doses or appointments
- Are not using substances in high-risk ways (including injecting drugs, having blackouts, etc)

SROM
Carries

- Up to 3 / wk
  - non-consecutive carries
  - Goal: maintaining treatment and building stability
- 4-6 / wk
  - clinically/socially stable;
  - minimum 12 weeks SROM
- Max 6 take-home doses secondary to lack of evidence

SROM: Harms of Carries

- Chewing or crushing the pellets can elease the entire morphine content as a bolus dose
- Co-ingestion with alcohol can also lead to rapid absorption of the dose.
- SROM can be crushed and dissolved for injection
- Injection drug use is associated with systemic viral infections such as Hepatitis C and HIV, soft tissue infections, bone and joint infections, infective endocarditis, vascular injury and thrombosis.
- IV use of SROM common in French OAT program and wide-spread diversion of SROM

Recommendation 6

- Take-home doses of based on clinical stability
  - Similar to methadone
- Start with non-consecutive carries
- Max of 6 carries for those on SROM ≥ 12w
- Care taken with those at high risk of diversion or altering route

Guideline Recommendations

RECOMMENDATION 1

SROM should be offered as a treatment option to individuals who have a diagnosis of OUD and are seeking OAT, within the context of a process for shared decision-making

RECOMMENDATION 2

Specific populations:

Severe OUD / high risk opioid use

Unacceptable side effects

Ongoing cravings or w/d without other OAT

High risk for prolonged QT or TdP

RECOMMENDATION 3

SROM starting doses should be based on the individual's opioid tolerance and risk of toxicity.

Can be as high as 200-400 mg for those with high tolerance

No maximum daily dose

Guideline Recommendations

RECOMMENDATION 4

Cross-tapering may be more appropriate than an abrupt stop and start transition between OAT medications.

The usual dose of Methadone: SROM is between 1:6 and 1:8

RECOMMENDATION 5

Missed doses: No dose adjustment for three consecutive missed doses

Reduction of 50% or to an initiation dose (whichever is higher) after four consecutive missed doses

RECOMMENDATION 6

Take-home doses: We recommend utilizing the same approach with SROM as with take-home doses of methadone

Patient Decision Tool

	Buprenorphine		Methadone	Kadian
	Suboxone	**Sublocade**		
How fast can I increase my dose?	The dose can be increased every day	There is one standard dose of the injection	The dose can be increased every three to five days	The dose can be increased every two days
When will I start feeling better?	You can usually get to a helpful dose within a few days if you start it in withdrawal	You will probably already be at a good dose from the tablets when you get your first injection	It can take one to two weeks to start feeling better, and one month to reach a dose that feels really helpful	It can take one to two weeks to start feeling better, and one month to reach a dose that feels really helpful
How do I get it?	Many health care providers prescribe it and most pharmacies have it	Not all health care providers do injections – you might have to go to a special clinic	Not all health care providers prescribe it, and not all pharmacies have it – you might have to go somewhere new, especially if you live in a small or remote area	Not all health care providers prescribe it for OAT, but most pharmacies have it – you might have to go somewhere new, especially if you live in a small or remote area
How much does it cost?	About $10–12 per day (covered by Ontario Drug Benefits)	$550 per month (covered by Ontario Drug Benefits with a Limited Use code)	About $6 per day (covered by Ontario Drug Benefits)	Varies by dose – an average dose (about 800 mg) would be about $21 per day (covered by Ontario Drug Benefits)
What are the side effects?	All opioids can cause sweating, constipation, dry mouth, headache, itchiness, and weight gain as side effects All opioids can cause hormone changes, which could lead to a lower sex drive, irregular periods, erectile dysfunction, or a higher chance of getting pregnant Kadian and methadone can both make you feel sedated or high at higher doses Buprenorphine has the mildest side effects (although the injection can leave a bump on the skin and can cause brief pain and itchiness on the belly) Kadian's side effects are mostly milder than methadone's			
What are the risks?	All opioid medications (especially methadone) can affect how other medications work – make sure you tell your health care provider about everything you're taking Methadone and Kadian both have a risk of overdose, especially when taken with alcohol or benzos (like Xanax or Valium) Methadone can be dangerous for people with certain kinds of heart problems (mostly related to irregular heart rhythms)			

	Buprenorphine		Methadone	Kadian
	Suboxone	**Sublocade**		
	Sublocade isn't recommended as a first choice for people who are pregnant			
How well does it work?	Buprenorphine is a "partial" opioid agonist – it might not fully relieve your withdrawal and cravings, especially if you have very high opioid tolerance If Sublocade isn't enough by itself, you can take Suboxone at the same time		Methadone and Kadian are both full opioids – they may be more likely than Suboxone or Sublocade to fully relieve withdrawal and cravings	
What would happen if I used opioids while taking it?	Blocks the high from other opioids more than methadone and Kadian	Blocks the high from other opioids more than methadone and Kadian	Reduces the effect of other opioids	Reduces the effect of other opioids

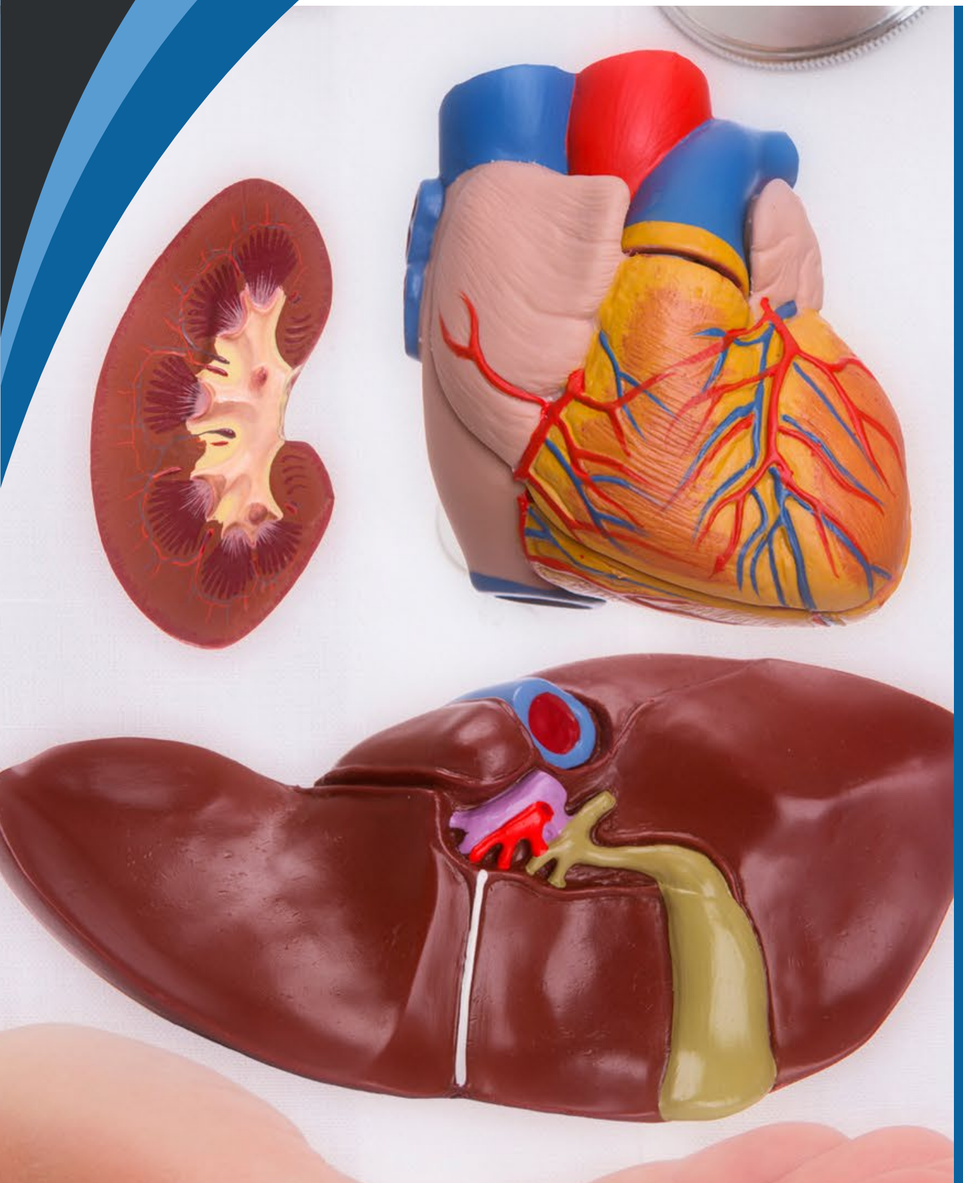
Your Feelings: OAT

	Not important	Somewhat important	Very important
Not having to go to the pharmacy every day			Suboxone/Sublocade
Taking a medication with a lot of evidence			Methadone/Suboxone
Taking a cheaper medication			Methadone
Not being in withdrawal before starting			Methadone/Kadian
Increasing my dose quickly			Kadian/Suboxone
Fewer side effects			Suboxone/Sublocade
Fewer risks			Suboxone/Sublocade
Less stigma			Kadian/Suboxone/Sublocade
Not having to go to a special clinic or pharmacy for my medication			Suboxone
Being able to get high from other opioids			Methadone/Kadian

Knowing about the differences between the three medications is an important start. Most people also have their own preferences, concerns, and values that will help them decide. How much do these things matter to you?

Thank You

About You: OAT



There are some things about your health and life that might affect yo decision. Go through these questions with your health care provider to see if any of the options might be a problem for your health:

Do you have any problems with your liver?

Do you drink alcohol?

- Yes - not a good candidate for SROM

Do you have any problems with your heart?

Do you take benzos (like Valium, Xanax, or Ativan)?

- Yes - may not be a candidate for SROM

Do you have any problems with your kidneys?

- Yes - not a good candidate for SROM