Slow-release oral morphine as MOUD: used internationally but why not the USA?

Jeremy Weleff, Gabriela Garcia, Mohit Singh, Andrew Saxon

ASAM 2023

Disclosure Information (Required)

- Jeremy Weleff, DO
  - “No Disclosures”
- Gabriela Garcia, MD
  - “No Disclosures”
- Mohit Singh, MD
  - “No Disclosures”
- Andrew Saxon, MD
  - Royalties, UpToDate, Inc. Section Editor

Overview

- Speaker introductions
- Brief overview of where we are today in the age of fentanyl.
- Introduction to slow-release oral morphine with a brief review of its pharmacology.
- Learning objectives →

- **Dr Gabriela Garcia:** Review of the core literature and international body of research on slow-release oral morphine and published clinical guidelines for OUD. Using a harm reduction lens, she will frame the discussion about expanded use of this medication in the USA.

- **Dr Mohit Singh:** Case examples of current clinical use of slow-release oral morphine in Canada during methadone inductions, switching from methadone to buprenorphine, and as monotherapy for OUD.

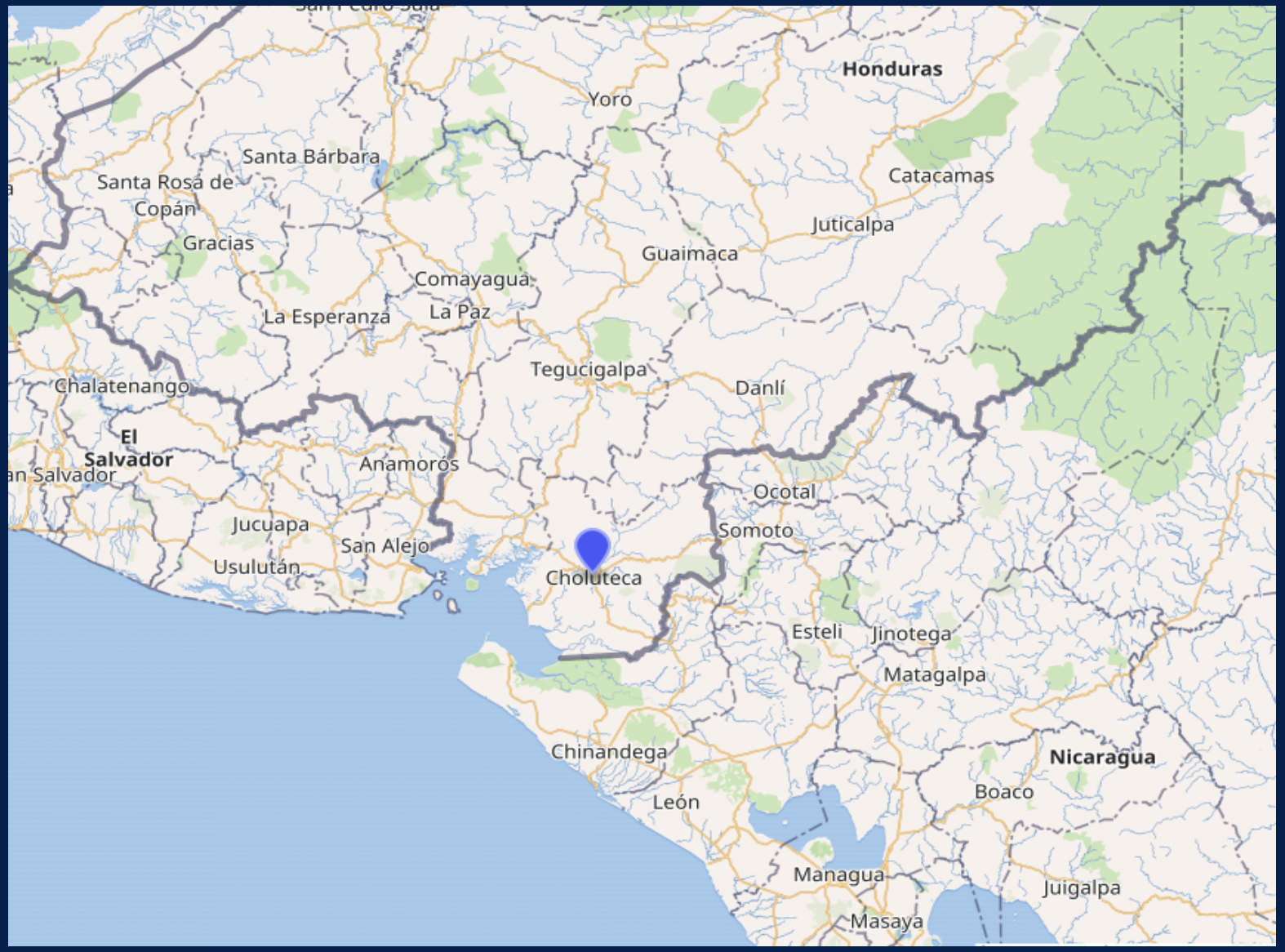
- **Dr Andrew Saxon:** Overview of the regulatory and policy issues that arise (or would arise) in the USA as we think about expanding use of slow-release oral morphine for OUD. He will discuss what would be needed for the USA to finally adopt this as another treatment option for OUD.

Learning Objectives

- Upon completion, participants will be able to describe the pharmacology and clinical evidence for the use of slow-release oral morphine for treatment of opioid use disorder.
- Upon completion, participants will be able to demonstrate knowledge about the clinical evidence for the use of slow-release oral morphine in methadone inductions, MOUD switches to buprenorphine, and as monotherapy for OUD.
- Upon completion, participants will be able to describe the regulatory and policy issues that impact the use of slow-release oral morphine in the USA.

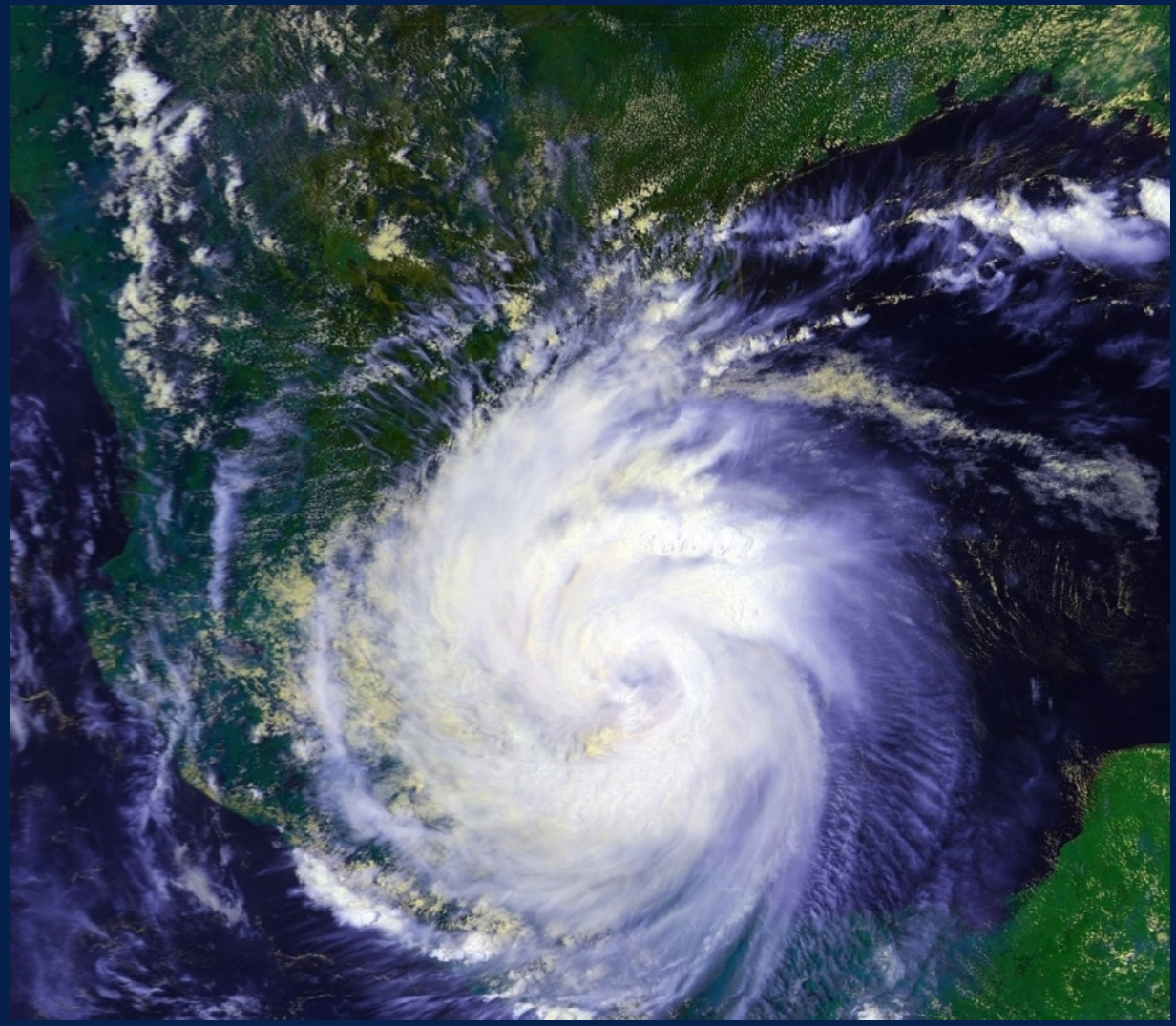
Every System is Perfectly Designed to get the Outcomes that it gets

Choluteca Bridge



1998 – a great feat of engineering

1998 – Hurricane Mitch comes along…



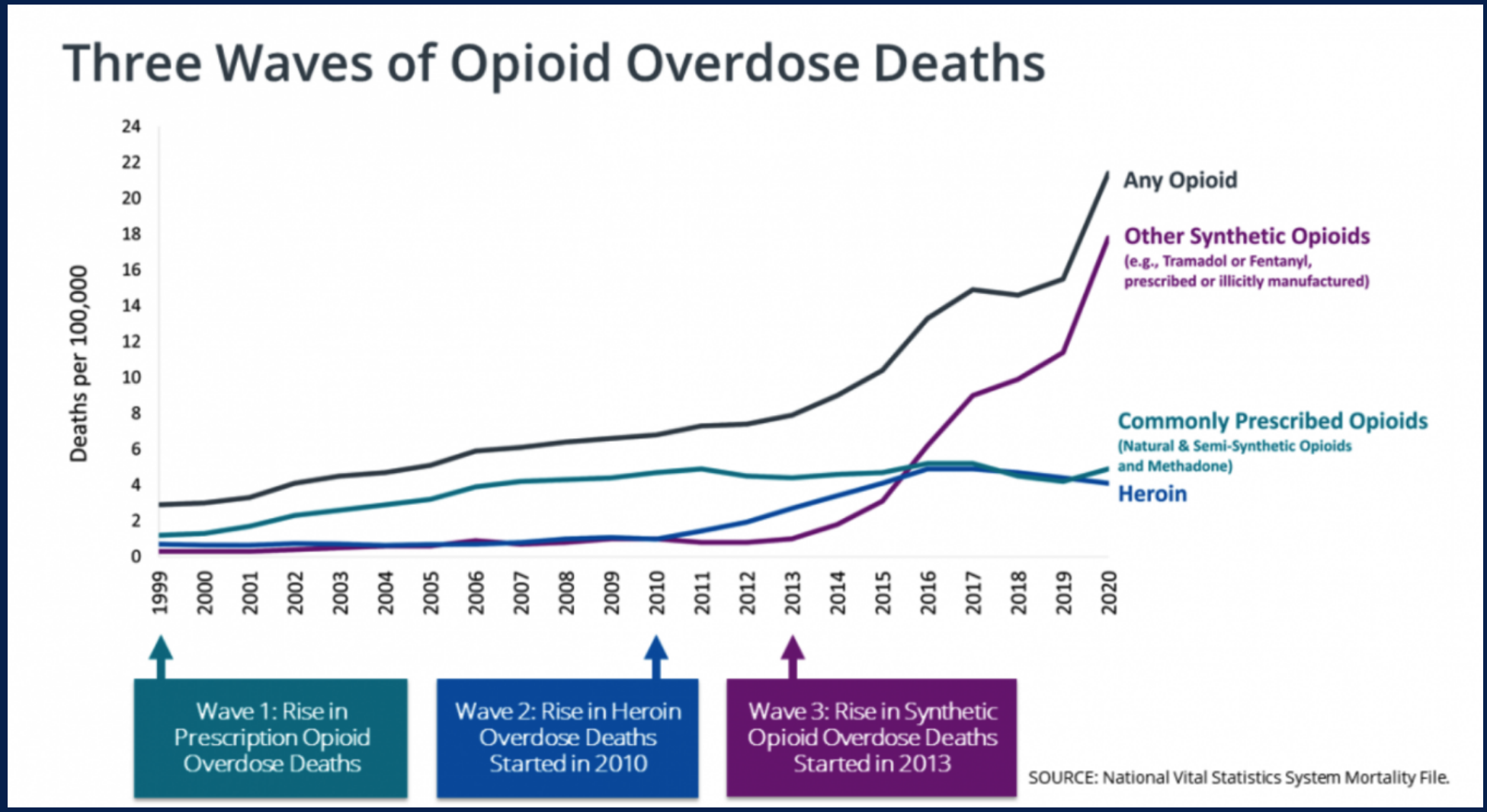
And the bridge survives completely intact…

The river moved…

The bridge looks great.

“The Bridge to Nowhere”

This is our system…



https://www.cdc.gov/opioids/basics/epidemic.html

Many hurricanes and a river of fentanyl…

Int J Drug Policy. Author manuscript; available in PMC 2020 Dec 1.
PMCID: PMC6914257
Published in final edited form as:
NIHMSID: NIHMS1543668
Int J Drug Policy. 2019 Dec; 74: 76–83.
PMID: 31563098
Published online 2019 Sep 25. doi: 10.1016/j.drugpo.2019.09.003

"Everything is not right anymore" Buprenorphine experiences in an era of illicit fentanyl

Sydney M. Silverstein,[a] Raminta Daniulaityte,[b] Silvia S. Martins,[c] Shannon C. Miller,[d,e] and Robert G. Carlson[f]

Our continued slow response/rigid framework is the Choluteca bridge…

10 years in and:

- **Relatively unchanged regulatory frameworks**
- **Slow uptake re: Harm Reduction**
- **Limited innovative/new drugs or treatments**
- **Starting MOUD; Buprenorphine inductions (low dose, high dose, etc)**

And are we already behind?

Most Recent Recommendations from Q1 2023

Benzodiazepines		Opioids		Stimulants & Hallucinogens		Synthetic Cannabinoids	
TIER ONE *(STRONGLY RECOMMEND)*							
Etizolam	1-10	N-Desethyl Isotonitazene⬆	<1	NN-Dimethylpentylone	>10	MDMB-4en-PINACA	<1
Flualprazolam	1-10	Isotonitazene	<1	Pentylone	>10	ADB-BINACA (-BUTINACA)	<1
Bromazolam	1-10	Metonitazene	<1	Eutylone	>10	ADB-5'Br-BINACA	<1
Flubromazepam	1-10	o/m/p-Fluorofentanyl	1-10	N-Propyl Butylone	>10	CH-PIATA⬆	<1
Clonazolam	<1	Carfentanil	<1	alpha-PHP / alpha-PiHP⬆	>10	ADB-FUBIATA	<1

- Center for Forensic Science Research and Education (CFSRE) laboratory recommendations for the detection of novel psychoactive substances (NPS) in the USA

https://www.cfsre.org/nps-discovery/scope-recommendations

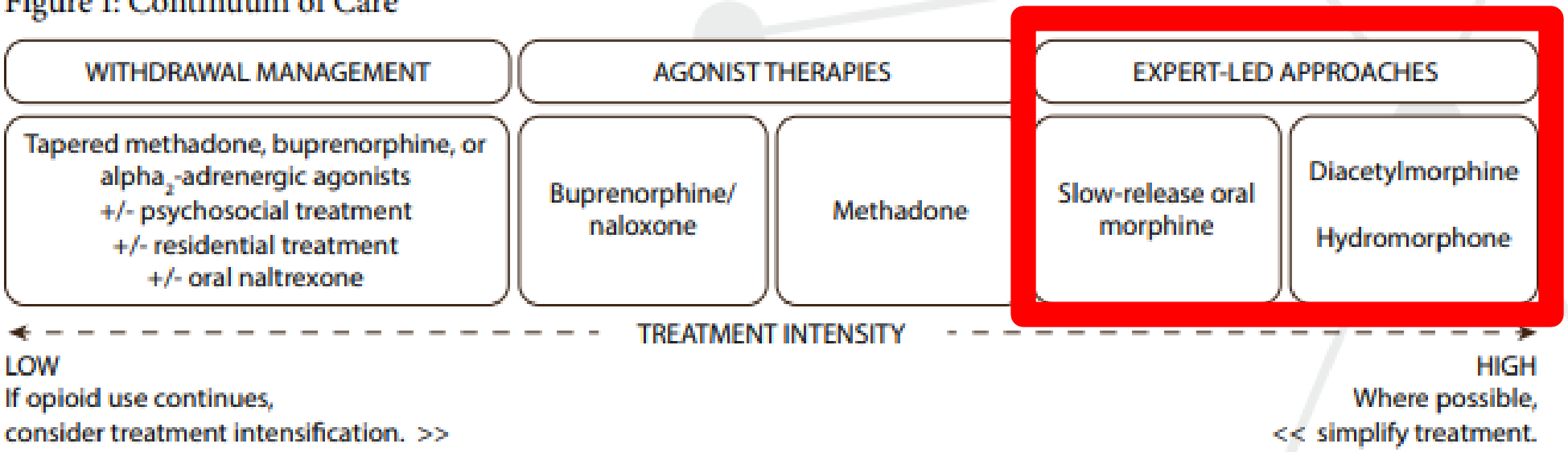
Opportunities and the future - USA

All of these many “structures” within the system that gives us these currently undesired outcomes in the age of fentanyl / the Opioid Epidemic

- Regulatory frameworks around treatment
  - X-Waiver recent example ; Other barriers to addiction care + OTPs etc.
- Harm Reduction / Safe Consumption
- Medications for OUD (novel and repurposed)
  - TODAY’S FOCUS: Slow-release oral morphine (SROM)

Slow-release oral morphine (SROM)

Figure 1: Continuum of Care



HARM REDUCTION	Across the treatment intensity spectrum, evidence-based harm reduction should be offered to all, including: • Education re: safer use of sterile syringes/needles and other applicable substance use equipment • Access to sterile syringes, needles, and other supplies • Access to Supervised Injection Sites (SIS) • Take-Home-Naloxone (THN) kits

BCCSU Guideline iOAT Guidelines -- https://www.bccsu.ca/wp-content/uploads/2021/07/BC_iOAT_Guideline.pdf

SROM pharmacology / history

- Slow-release oral morphine (SROM) is a 24-hour slow-release formulation of morphine that, like other treatments for OUD acts at the μ-opioid receptor.
- Launched in Australia in 1994 and in the United States in 1996. It currently is marketed as KAPANOL in Europe, Africa, Asia, Australia and New Zealand, and as KADIAN in the United States, Canada and Japan.
- KADIAN (morphine sulfate extended-release) Capsules, a formulation of extended-release morphine sulfate that is indicated for q24 h or q12 h dosing in the United States

A place for SROM

- Since the early 2000s, there has been growing evidence for the use of SROM as a therapeutic agent for OUD [7-13] and it continues to be included in international treatment guidelines for OUD.[14-17]

- Evidence from systematic reviews and meta-analyses of randomized trials have shown that SROM has comparable efficacy to methadone and buprenorphine regarding treatment retention and opioid use with favorable tolerability.[18-20] Particularly effective for those that have failed available first line treatments such as methadone.[12,13]

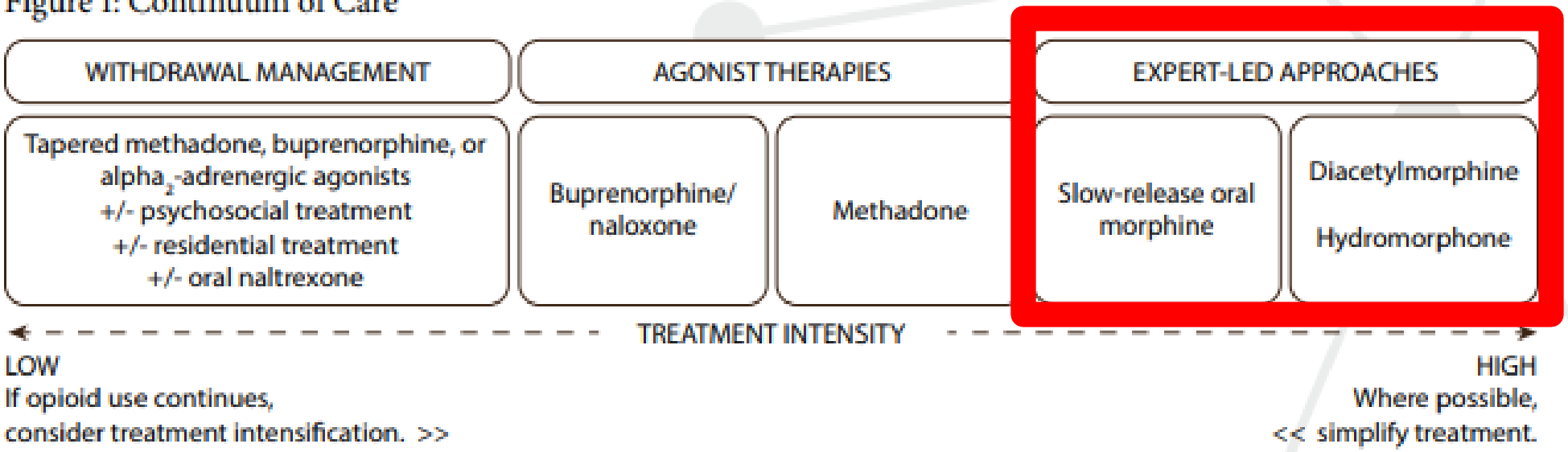
- Despite this evidence, to date there have been no completed trials of SROM in the United States for OUD.

A place for SROM

- Pharmacology allows it to be dosed once daily
- Relatively short time to steady state ; shorter half-life than methadone
- Fits a unique space within our armamentarium
  - Bridging methadone to buprenorphine
  - Augmenting methadone inductions
  - Even sometimes as monotherapy (limited data)

Slow-release oral morphine (SROM)

Figure 1: Continuum of Care



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BCCSU Guideline iOAT Guideliens -- https://www.bccsu.ca/wp-content/uploads/2021/07/BC_iOAT_Guideline.pdf

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Gabriela Slides

- Dr Garcia will then present the international body of research on slow-release oral morphine including past and recently published clinical guidelines for OUD that include its use. She will also review the results of a Cochrane systematic review and metanalysis and other core articles describing the use of slow-release oral morphine in OUD. Using a harm reduction lens, she will frame the discussion about expanded use of this medication in the USA.

SROM: Clinical Approaches

- Dr Singh & Dr. Wang will describe the current, practical clinical use of slow-release oral morphine in Canada: Case examples from his personal practice including and as monotherapy for OUD, SROM induction and titration, switching from methadone to buprenorphine & combination use in injectable opioid agonist treatment.

- Learning objective #2: Upon completion, participants will be able to demonstrate knowledge about the clinical evidence for the use of slow-release oral morphine in methadone inductions, MOUD switches to buprenorphine, and as monotherapy for OUD.

Case A: Inpatient SROM Induction

- 43y F with opioid withdrawal admitted for osteomyelitis
- Daily use of fentanyl (1 g/day) and methamphetamine
- Recently switched methadone 180 mg (prolonged QT) to buprenorphine/nal, lost to follow up, overdosed
- Agreed to start SROM

Case A: Inpatient SROM Induction

- Day 1:
  - SROM 24H 200 mg PO daily in AM
  - Morphine 40-80 mg PO q1h PRN → used 560 mg
  - Nursing: open capsule, mix granules with applesauce or yogurt, directly witnessed ingestion, monitor for oversedation during day
- Day 2:
  - SROM 24H 400 mg PO daily in AM
  - Morphine PRN → used 480 mg

Case A: Inpatient SROM Induction

- Day 3:
  - SROM 24H 500 mg PO daily in AM
  - Morphine PRN → used 320 mg
- Day 4:
  - SROM 24H 600 mg PO daily in AM
  - Morphine PRN → used 160 mg
- Day 5:
  - SROM 24H 700 mg PO daily in AM
  - Morphine PRN → used 80 mg

Case A: Inpatient SROM Induction

- Day 6:
  - SROM 24H 700 mg PO daily in AM
  - Morphine PRN → used 120 mg
- Day 7:
  - SROM 24H 800 mg PO daily in AM
  - Morphine PRN → used 40 mg
- Continue on SROM 24H 800 mg daily
  - Morphine PRN → used 0-80 mg/day
- Discharge on SROM 24H 800 mg daily when off IV antibiotics

Case A: Inpatient SROM Induction

- Variations
  - Higher or lower starting dose
  - Slower titration every 2 days or smaller increments
  - Faster titration if tolerance known
  - Hydromorphone PRN
  - Same-day top-up SROM dose

Case B: Outpatient SROM Restart

- 28y M OUD at Rapid Access Addictions Clinic (hospital-based walk-in substance use clinic) to restart SROM 24H
- Remission on 1200 mg/day for 10 months, relapsed, smoked fentanyl 0.1 g twice
- Last dose 6 days ago (missed 5 days) → re-induction
- UDS: + fentanyl, + opiates, + benzodiazepines, + THC

Case B: Outpatient SROM Restart

- Standard re-induction
  - SROM 24H 200 mg PO daily in AM, dose given at clinic
  - 1-week prescription given for directly witnessed ingestion at community pharmacy
  - Instructed to return in 1-2 days
  - Titrate up by 100-200 mg increments until stable
  - In province of BC, can prescribe hydromorphone PRN for withdrawal, daily dispensed at community pharmacy (harm reduction)

Case B: Outpatient SROM Restart

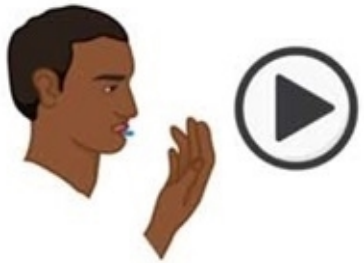
- New rapid titration protocol (Vancouver, St. Paul's Hospital RAAC)
  - Monitor in short stay area of clinic (5 reclining chairs, food, water, low stimulation environment, frequent nursing assessment)
  - Morphine 200 mg PO (1st dose), assess response
  - Morphine 200 mg PO (2nd dose), assess response
  - Morphine 100 mg PO (3rd dose), assess response
  - Prescription for SROM 12-H 500 mg PO x 1 in evening
  - Return next AM for assessment, start SROM 24H 1000 mg daily

Case C Outpatient SROM: Bupe Induction

- 40-year-old F, OUD early remission, 100 mg methadone for 3 months and stable.
- Job requires longer periods of travel, experiencing low grade side effects from methadone. Wants to switch to Buprenorphine.

Ghosh

Case C: Outpatient SROM Bridge

Day 0	Day 1	Day 2-5	Day 6	Day 7
				
Last dose of methadone in the AM	24hrs after last methadone dose, transition to 1:4 ratio of STROM	Increase SROM ratio as needed to help with withdrawals and cravings	Last single dose of SROM in the morning	24hrs after last SROM dose, induce buprenorphine

A Review of Novel Methods To Support The Transition From Methadone and Other Full Agonist Opioids To Buprenorphine/Naloxone Sublingual In Both Community and Acute Care Settings, Ghosh et al., 2019. Canadian Society of Addiction Medicine.

Case D Outpatient SROM: Micro-induction

40-year-old M, unable to stabilize on methadone 125 mg. Unable to titrate due to elevated QTc. Continues to use illicit Fentanyl. Open to Buprenorphine trial. Not wanting to endure withdrawal symptoms. Not wishing to go to detox.

Consider R/B of micro-induction with SROM vs. Methadone

Case D Outpatient SROM: Micro-induction

Switch to SROM & Bernese Method (different variations)

	Buprenorphine	SROM
Day 0	Stop Methadone	----------
Day 1	0.5 mg SL BID	500 mg (1:4)
Day 2	1 mg SL BID	600 mg
Day 3	2 mg SL BID	700 mg
Day 4	3 mg SL BID	700 mg
Day 5	4 mg SL BID	700 mg
Day 6	12 mg SL daily + 4 mg SL PRN	Stop SROM
Day 7	Consolidate once daily & Titrate to effective dose	----------

Also, an option for those with active opioid use with no OAT

Ghosh et al., Can J Addict 2019;10: 41-50 & Ghosh SM, Lim R, Yu A, et al, Can J *Addict* 2019;10:18–24

Alternative Uses of SROM: Augment

Methadone induction w/ SROM

- Augment use of SROM: methadone induction & titration of methadone to stable dose
- Guidance based on clinical experience; *no clinical trials have been published* to inform definitive practice guidelines
  - Fentanyl Use Disorder

Meta: Phi Fentanyl Use Disorder Guidelines, 2021
CAMH OUD guidelines, 2021

Alternative Uses of SROM: Augment

Case: Methadone & SROM

- 35-year-old M, presents to clinic, previous stability at Methadone 120 mg but lost to follow up. Now, unable to titrate back to stable dose of methadone despite multiple attempts.

Ongoing Fentanyl use and reports inadequate starting doses of Methadone as well as withdrawal/craving as reasons for non-adherence.

Induction:

Methadone 30 mg daily & SROM 100-200 mg po daily (DWI)

Titration:

- Methadone 10 mg q3days to stable dose
- SROM 50–100mg per visit (during titration of methadone)

Maintenance:

SROM 100–300mg po daily (clinical variation)

Taper:

Consider R/B: i.e., consider patient response & clinical factors

Meta: Phi Opioid Guidelines, Bromley et al 2021

Alternative Uses of SROM: iOAT

- Injectable Opioid Agonist Treatment

	Recommendation	Quality of Evidence	Strength of Recommendation
Injectable Opioid Agonist Treatment			
1.	Injectable opioid agonist treatment should be considered for individuals with severe, treatment-refractory opioid use disorder and ongoing illicit injection opioid use.	Moderate	Conditional
Medication Selection			
2.	For patients who are determined to be likely to benefit from injectable opioid agonist treatment, both diacetylmorphine and hydromorphone are acceptable treatment options.	Low	Strong
Treatment End Date			
3.	Injectable opioid agonist treatment should be provided as an open-ended treatment, with decisions to transition to oral OAT made collaboratively with the patient.	Low	Strong

The patient attends clinic **2-3** times per day for a **supervised injection**

Combined with an oral therapy such as methadone or SROM (long acting)

"Low-volume, high intensity"

CRISM iOAT guidelines, 2019

Alternative Uses of SROM: iOAT

Case: 50-year-old M, severe injection Fentanyl Use Disorder. Instability on Bupe, Methadone, SROM monotherapy.

Now stable iOAT:

HM 110 mg IV TID

SROM 400 mg po daily

<u>SROM</u>**:**

Start: 100-200 mg, increase by 50-100 mg q1-2 days (max 1200mg/day). Titrate with injectable.

Target: no withdrawal sx between doses.

Adding SROM may reduce iOAT dose & frequency of daily injections over time

CRISM iOAT guidelines, 2019

BCCSU, Clinical Update, 2022

Summary: Clinical Uses

- SROM is an effective 3rd line monotherapy for OUD
- Offers option of rapid titration to effective dose in Fentanyl Use Disorder
- Outpatient (& inpatient) option for induction of Buprenorphine
- Can be used in combination with other OUD tx on/off label (iOAT, Augment for Methadone induction)
- Limitations: Aside from use as monotherapy: no efficacy trials done & limited data (smaller studies, case series). More research to come.

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Ghosh et al., 2019. A Review of Novel Methods To Support The Transition From Methadone and Other Full Agonist Opioids To Buprenorphine/Naloxone Sublingual In Both Community and Acute Care Settings. *Can J Addict* 2019;10: 41-50

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Regulatory Steps to Approval of SROM to Treat OUD in U.S.

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Center of Excellence in Substance Addiction Treatment and Education
VA Puget Sound Health Care System

ASAM Annual Meeting, April 14, 2023

Disclosure Information (Required)

Slow-release oral morphine as MOUD: used internationally but why not the USA?

April 14, 2023, 3 p.m.

Andrew J. Saxon, MD

- Royalties, UpToDate, Inc. Section Editor

Learning Objectives

- Understand some of the regulatory steps necessary for FDA to approve a new medication for treatment of opioid use disorder

Steps to Achieve FDA Approval of SROM

- Sponsor
- Choose formulation
- Investigational New Drug (IND) Application to FDA
- File New Drug Application (NDA) to FDA

JAMA
THE JOURNAL of the
American Medical Association
May 24, 1971 Vol 216, No. 8

Methadone and *l*-Methadyl Acetate

Use in Management of Narcotics Addicts

Jerome H. Jaffe, MD, and Edward C. Senay, MD

Ten volunteer patients participating in a methadone hydrochloride maintenance program were assigned randomly to experimental (five patients) or control (five patients) groups. These patients had been in treatment for several months and had been stabilized (had no change of dose for at least three weeks) with methadone prior to inclusion in the study. Patients in the experimental group were given l-methadyl acetate (l-α acetylmethadol) on weekends and methadone on weekdays. Patients in the control group were given methadone each day. Clinic attendance, requests for change in medication, and scores on an opiate-withdrawal test instrument did not reveal differences between groups. Clinical observers blind to the experiment were unable to discriminate experimental and control patients. No untoward reactions were observed in either group. These preliminary observations suggest that l-methadyl acetate can be interchanged repeatedly with methadone without difficulty.

medication from five to seven days each week. Since methadyl acetate suppresses the narcotic withdrawal syndrome even when administered as infrequently as three times per week, the travel problems of patients just starting treatment are markedly decreased. Second, and of equal importance, is the possibility of reducing illicit redistribution of the maintenance medication. When patients come to clinics for methadone less frequently than every day, the clinics must permit them to take medication for use at home. In any large-scale program, it is inevitable that a few patients will abuse this opportunity and give away or sell their medication. In addition, there is a possibility that a patient's medi-

Human Pharmacology and Abuse Potential of the Analgesic Buprenorphine

A Potential Agent for Treating Narcotic Addiction

Donald R. Jasinski, MD; Jeffrey S. Pevnick, MD; John D. Griffith, MD

• **Buprenorphine was evaluated for its abuse potential and utility in treating narcotic addiction. The drug was morphine-like but was 25 to 50 times more potent than morphine and was longer-acting. Little if any physical dependence of clinical significance was produced by buprenorphine. The effects of morphine to 120-mg doses were blocked by buprenorphine, a blockade that persisted for 29½ hours. In man, buprenorphine has less intrinsic activity than morphine, and as such, has a low abuse potential. Moreover, the drug has potential for treating narcotic addiction since it is acceptable to addicts, is long-acting, produces a low level of physical dependence such that patients may be easily detoxified, is less toxic than drugs used for maintenance therapy, and blocks the effects of narcotics.**

(*Arch Gen Psychiatry* 35:501-516, 1978)

Buprenorphine hydrochloride is a clinically effective analgesic some 25 to 40 times more potent than morphine sulfate.[1] The drug is a highly lipophilic oripavine derivative containing a cyclopropylmethyl substitution (Fig 1) similar to that in the narcotic antagonists cyclazocine and naltrexone.[2] In rats, mice, and monkeys, bupre-

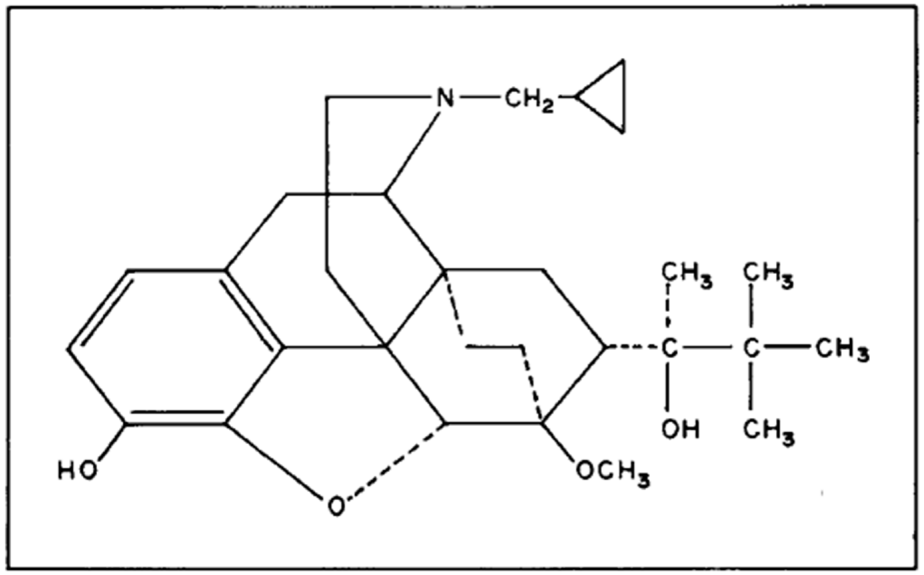

Fig 1.—Structure of buprenorphine (*N*-cyclopropylmethy/-7α-1-S-hydroxy-1, 2,2-trimethylpropyl)-6,14-endoethano-6,7,8,14-tetrahydronororipavine.

Accepted for publication Oct 15, 1977.

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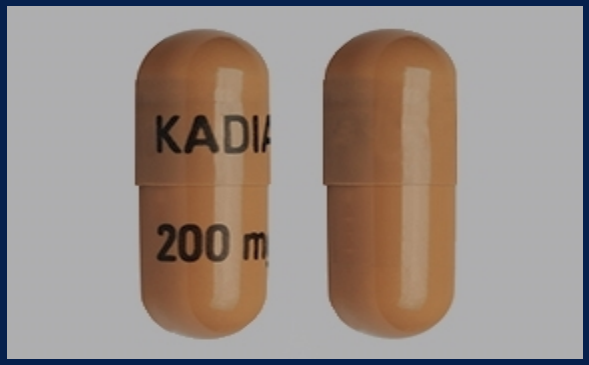
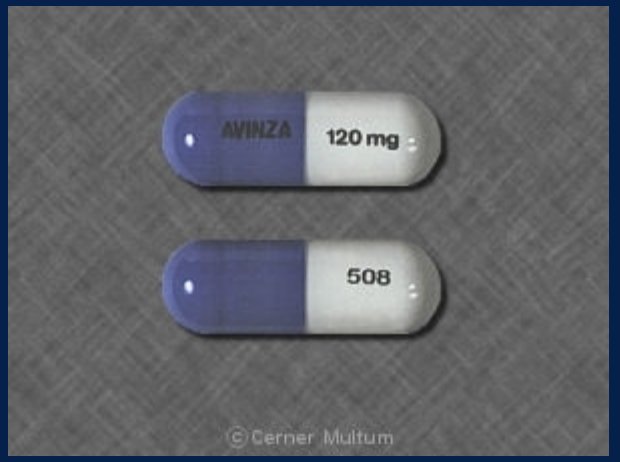
Sponsor

- Pharmaceutical Company?
- Foundation?
- NIH?
- Individual physician?

Formulation

- Because of need for sustained release formulation, cannot simply use a generic form of morphine
- Possibly 2 options
  - Kadian (Actavis/Alpharma)
  - Avinza (Pfizer; no longer marketed in the U.S.)





IND Application

- Animal Pharmacology and Toxicology Studies - Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans. Also included are any previous experience with the drug in humans (often foreign use).

- Manufacturing Information - Information pertaining to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed to ensure that the company can adequately produce and supply consistent batches of the drug.

- Clinical Protocols and Investigator Information - Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks. Also, information on the qualifications of clinical investigators--professionals (generally physicians) who oversee the administration of the experimental compound--to assess whether they are qualified to fulfill their clinical trial duties. Finally, commitments to obtain informed consent from the research subjects, to obtain review of the study by an institutional review board (IRB), and to adhere to the investigational new drug regulations.

NDA Application

- The goals of the NDA are to provide enough information to permit FDA reviewer to reach the following key decisions:
  - Whether the drug is safe and effective in its proposed use(s), and whether the benefits of the drug outweigh the risks.
  - Whether the drug's proposed labeling (package insert) is appropriate and what it should contain.
  - Whether the methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality, and purity.

NDA 505(b)

- One or more of the investigations relied upon by the applicant for approval "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted" (21 U.S.C. 355(b)(2)).

- **What type of information *can* an applicant rely on?**
  - Published literature
  - The Agency's finding of safety and effectiveness for an approved drug

- **What kind of application can be submitted as a 505(b)(2) application?**
  - New chemical entity (NCE)/new molecular entity (NME)
  - Changes to previously approved drugs

- **WHAT ARE SOME EXAMPLES OF 505(B)(2) APPLICATIONS?**
  - *Indication*. An application for a not previously approved indication for a listed drug.

Final Takeaways/Summary (Suggested)

- Getting FDA approval for slow-release oral morphine to treat opioid use disorder is likely to be a long and complex process

References (Required)

1. https://www.fda.gov/media/156350/download
2. Jaffe JH, Senay EC. Methadone and l-methadyl acetate. Use in management of narcotics addicts. JAMA. 1971 May 24;216(8):1303-5. PMID: 5108447.
3. Jasinski DR, Pevnick JS, Griffith JD. Human pharmacology and abuse potential of the analgesic buprenorphine: a potential agent for treating narcotic addiction. Arch Gen Psychiatry. 1978 Apr;35(4):501-16. doi: 10.1001/archpsyc.1978.01770280111012. PMID: 215096.

- Current barriers to prescribing*
- The need for a North American (USA?) trial on SROM
- Next steps for research / advocacy / regulation change

- Imagining an American implementation of SROM
  - Limited to addiction specialists*
  - Limited to OTPs for observed doses(?)
  - Opening up prescribing of this medication for OUD to all prescribers

Final Takeaways/Summary (Suggested)

References (Required)

1. Socias, M. E., Wood, E., Dong, H., Brar, R., Bach, P., Murphy, S. M., & Fairbairn, N. (2020). Slow release oral morphine versus methadone for opioid use disorder in the fentanyl era (pRESTO): Protocol for a non-inferiority randomized clinical trial. Contemporary clinical trials, 91, 105993. https://doi.org/10.1016/j.cct.2020.105993

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