# Methadone Initiation for Opioid Use Disorder in the Emergency Department

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Matthew Salzman, MD, MPH – Cooper Medical School of Rowan University
William E. Soares, III, MD, MS – UMASS Chan Medical School - Baystate
Ryan P. McCormack, MD, MS – NYU Grossman School of Medicine
Jessica Heil, MPH – Cooper University Health Care

# Disclosure Information (Required)

- Rachel Haroz, MD – Cooper Medical School of Rowan University
  - No Disclosures
- Joseph D'Orazio, MD – Cooper Medical School of Rowan University
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- Matthew Salzman, MD, MPH – Cooper Medical School of Rowan University
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  - No Disclosures
- Jessica Heil, MPH – Cooper University Health Care
  - No Disclosures

# Learning Objectives

- Describe the pharmacologic properties, risks, and benefits of methadone treatment in OUD treatment.
- Understand the regulatory and geographic considerations of OTPs and their impact on ED-based methadone initiation.
- Apply ASAM Clinical Practice Guidelines to establish safe methadone dosing protocols for ED settings.
- Describe approaches reflective of different geographic, regulatory restrictions

# Poll

What is your primary occupation?

- Physician and APPs
- Psychologist
- Other Practitioners
- Counselors
- Peer Navigators
- Researchers or Academics
- Residents, Fellows, and Students
- Others

How would you describe the primary location where you currently practice medicine?

- Academic
- Community
- Federal

# Purpose

Translating OUD treatment initiation to the ED setting

Transformational Events:

1) The Opioid Epidemic
2) 2015:  Landmark study of ED-initiated buprenorphine

Original Investigation

**Emergency Department–Initiated Buprenorphine/Naloxone Treatment for Opioid Dependence**
A Randomized Clinical Trial

Gail D'Onofrio, MD, MS; Patrick G. O'Connor, MD, MPH; Michael V. Pantalon, PhD; Marek C. Chawarski, PhD; Susan H. Busch, PhD; Patricia H. Owens, MS; Steven L. Bernstein, MD; David A. Fiellin, MD


D' Onofrio et al JAMA. 2015;313(16):1636-1644; Bush et al.

# Why focus on the ED?

- … because that's where the patient's are!
- Logical point of intervention to narrow the treatment gap
- Resources now exist to support implementation, but  local champions are essential

# Why Methadone??

**We have buprenorphine, why do we also need methadone?**

Growing reluctance to transition to buprenorphine

- Evolving concerns and approaches in the fentanyl era
- Complicated buprenorphine initiations, including precipitated withdrawal
- Dose adequacy
- Choice and engagement

# The Gameplan

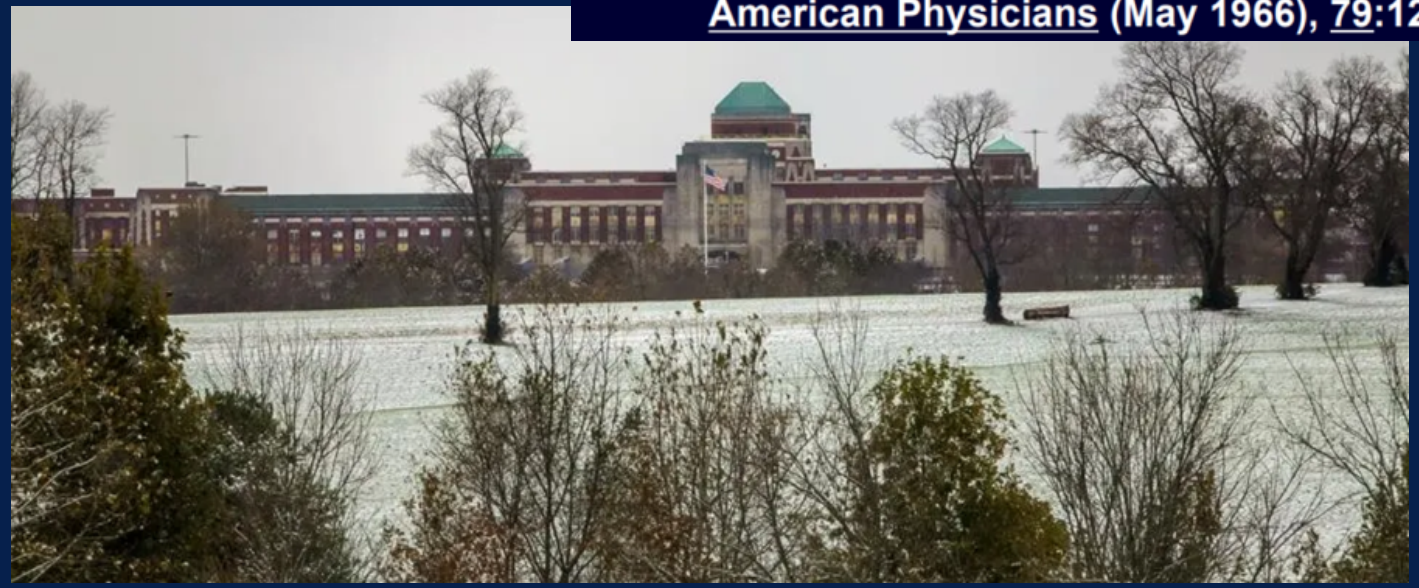
- History of regulations
- Commons misconceptions
- Methadone initiation
- Processes, infrastructure and leadership  for the ED
- Cases and panel discussion

# History of Methadone Treatment

Vincent P. Dole, Jr., MD; Marie Nyswander, MD; and Mary Jeanne Kreek, MD

**First research paper describing methadone maintenance treatment research**

Dole, V.P., Nyswander, M.E. and Kreek, M.J.: Narcotic blockade: a medical technique for stopping heroin use by addicts. Transactions of the Association of American Physicians (May 1966), 79:122-136, 1966. *(including discussion)*



# Opioid Treatment Programs

- *Methadone Clinic*
- *Federally regulated with state and county regulations superimposed – 5 tiers + 2 federal statutes*
- *Structure is rigid, difficult to access information*
- *Past Expectations: daily attendance, participation in counseling, programming – (finance…)*
- *Little consideration for employment, childcare, illness*

# History of Regulations

Harrison narcotic Act 1914

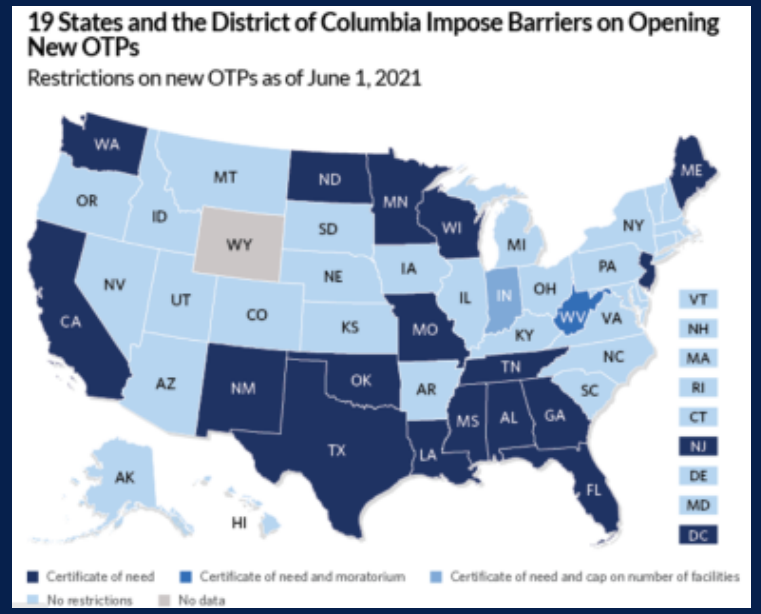
Federal Regulations of 1972 - Title 42 of the Code of Federal Regulations (42 CFR) part 8

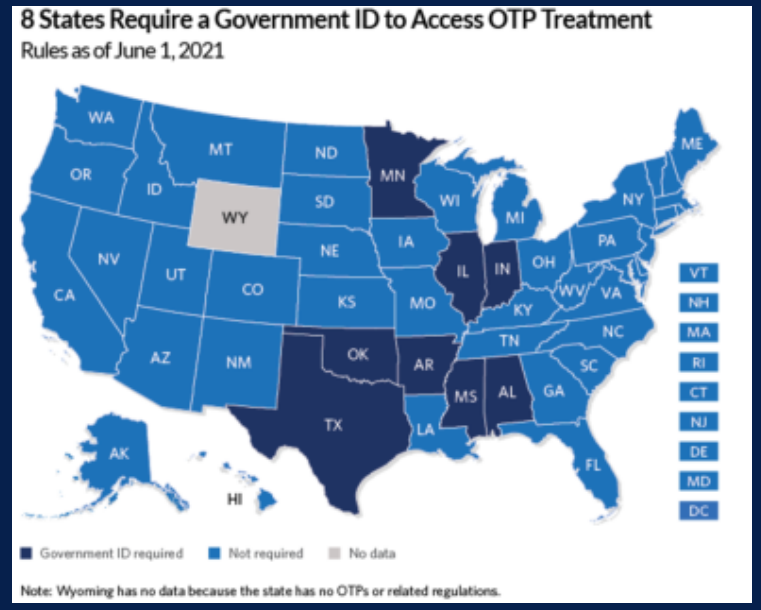
Oversight moved to SAMHSA 2001

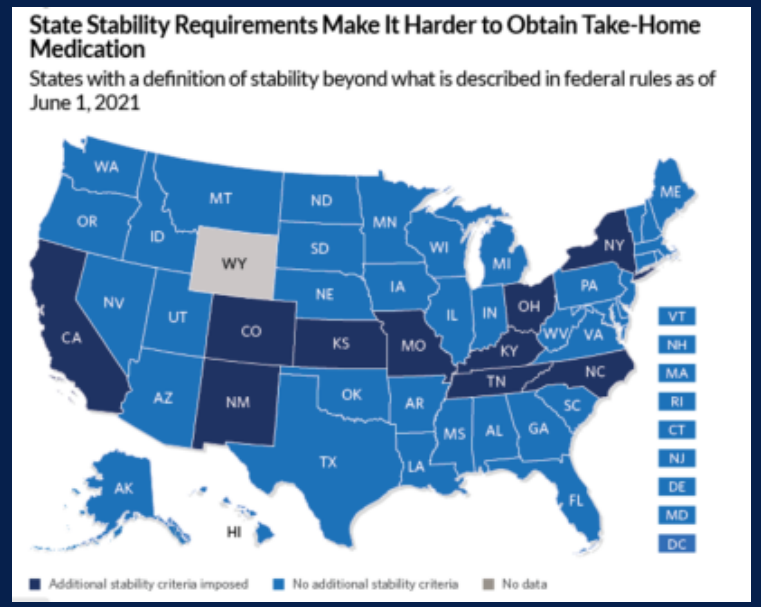
2020 COVID impact

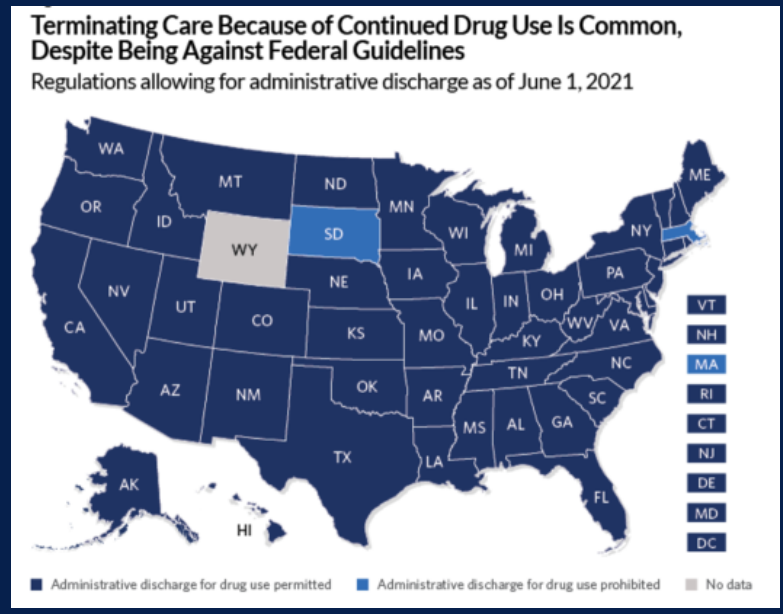
New Federal Regulations 2024

# Some State Differences




[Overview of Opioid Treatment Program Regulations by State | The Pew Charitable Trusts (pewtrusts.org)]

# PRESS RELEASES

*Home / Media / Press Releases*

## Reps. Norcross, Bacon Lead Introduction of the Modernizing Opioid Treatment Access Act

***March 6, 2023***

**WASHINGTON, DC** – Today, U.S. Congressmen Donald Norcross (D-NJ-01) and Don Bacon (R-NE-02) unveiled the Modernizing Opioid Treatment Access (MOTA) Act (H.R. 1359). This evidence-based legislation would increase access to care for people experiencing opioid use disorder (OUD) by reforming the outdated regulations governing the prescription and dispensing of methadone. Methadone is one of the most effective medicines used for the treatment of OUD and is considered an "essential medicine" by the World Health Organization. U.S. Representatives Annie Kuster (D-NH-02), David Trone (D-MD-06), Brain Fitzpatrick (R-PA-01), Paul Tonko (D-NY-20), Brittany Pettersen (D-CO-07), and Andy Kim (D-NJ-03) are original cosponsors of the bill.

"Improving access to treatment saves lives, period," **said Congressman Norcross**. "This legislation lowers barriers to care at a time when we are still suffering staggering losses due to the ongoing opioid epidemic. We must end the monopoly on this life-saving medicine that only serves to enrich a

# Misconceptions

https://methadonemisconceptions.my.canva.site/

# Misconceptions

Poll questions:

1. Emergency Departments are not allowed to administer more than 30 mg of methadone (T/F) for an initial dose.
2. An ECG must be obtained prior to methadone administration (T/F).
3. Short-acting opioid analgesics will have no benefit to patients on methadone maintenance (T/F).
4. A patient can be dosed in the Emergency Department for a maximum of three consecutive days (T/F).
5. Patients presenting to the Emergency Department for a missed methadone dose may only be given 40 mg regardless as to their clinic dose.
6. Patients who miss more than 3 days of methadone and present to the Emergency Department should be treated as new start and administered 30 mg of methadone.
7. A urine drug screen should be obtained prior to methadone administration in the Emergency Department.

ELSEVIER

The American Journal of Emergency Medicine

Volume 89, March 2025, Pages 209-215

# Emergency department utilization of the methadone "72-hour rule" to bridge or initiate and link to outpatient treatment

Samantha Huo MD, MPH, MS [a b], Jessica Heil MS [a], Matthew S. Salzman MD, MPH [a c d], Alice Ely PhD [a], Samuel Snyder [c], Dante Terracciano [c], Rachel Rafeq PharmD [d], Valerie Ganetsky PharmD [a], Gerard Carroll MD [d e], Rachel Haroz MD [a c d]

"At 30 days, 75 % of patients linked to our partner OTP were retained in treatment."

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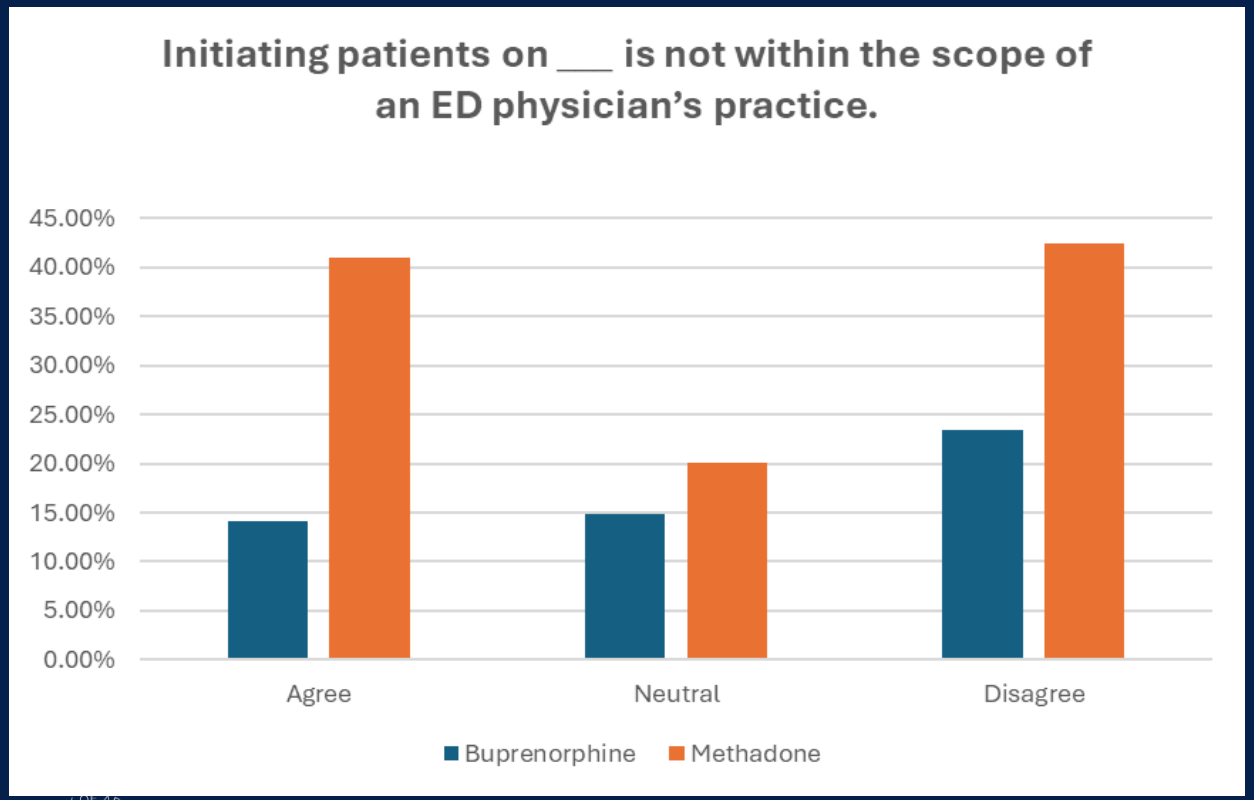
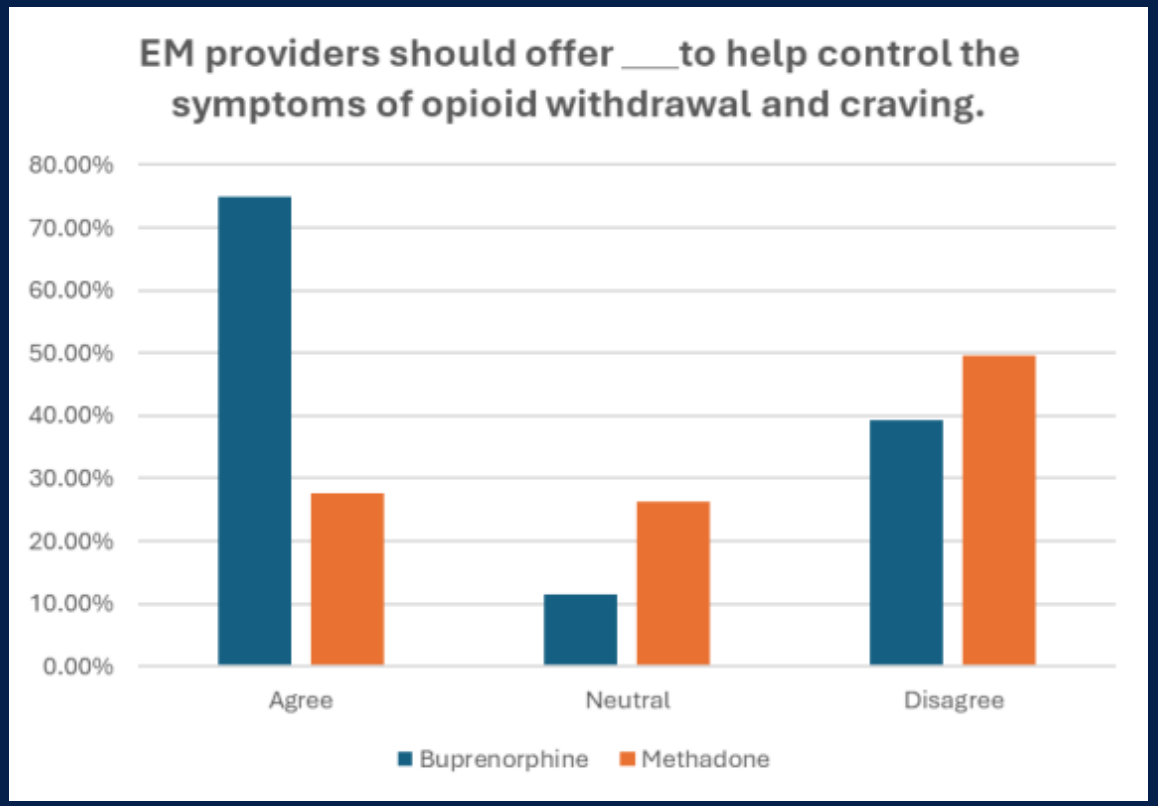
WestJEM
Integrating Emergency Care With Population Health

West J Emerg Med. 2022 Apr 4;23(3):386–395. doi: 10.5811/westjem.2022.2.54681

# Attitudes on Methadone Utilization in the Emergency Department: A Physician Cross-sectional Study

Jessica Heil, Valerie S Ganetsky, Matthew S Salzman, Krystal Hunter, Kaitlan E Baston, Gerard Carroll, Eric Ketcham, Rachel Haroz



# Methadone vs Buprenorphine or Naltrexone

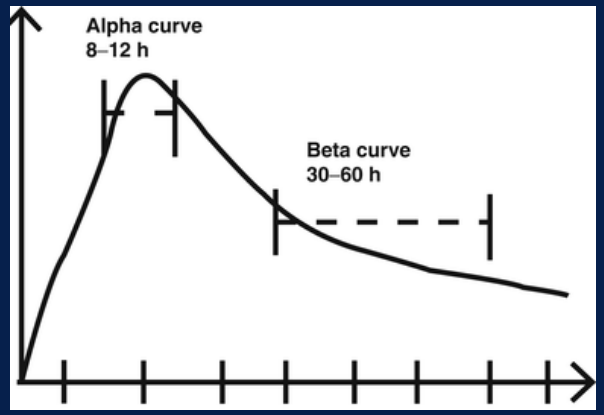
- Full opioid agonist: Effective for high-dependency cases
  - No ceiling effect (unlike buprenorphine).
  - Beneficial for patients with severe dependence, severe withdrawal intolerance, history of difficult buprenorphine inductions

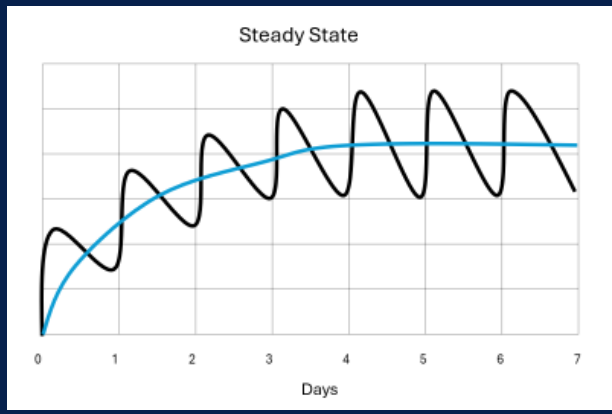
- Limitations:
  - Requires daily visits to an OTP (opioid treatment program).
  - QTc prolongation risks
  - Others

Murphy, 2024, American Journal of Drug & Alcohol Abuse
Englander et al., 2024, JAMA Internal Medicine

# Methadone Pharm

- Synthetic opioid, metabolized by liver, excreted in feces
  - High lipid solubility, redistributes in fat tissues
    - 5-7 days of dosing to reach steady-state
  - Long elimination half-life (average 24 hours, up to 60 hours)
    - Shorter duration of action/analgesic action (4-8)
  - Metabolised by CYP3A4 primarily, no active metabolites
    - Rifampin (potent CYP3A4 inducer) decreases methadone levels by increasing metabolism (Others include phenytoin, phenobarbital, carbamazepine, and St John's Wort)
    - Rapid metabolizers with CYP3A4 polymorphisms

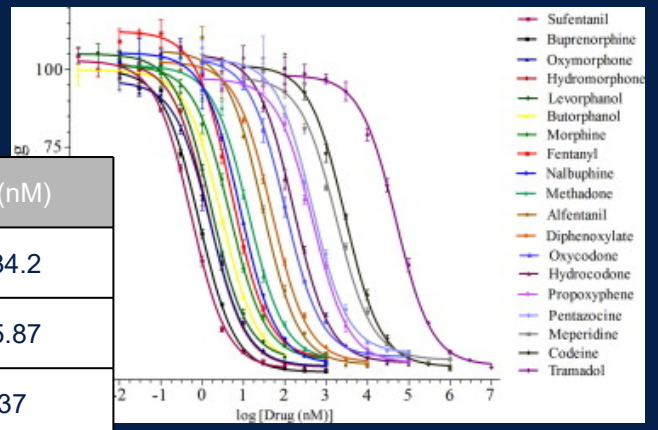


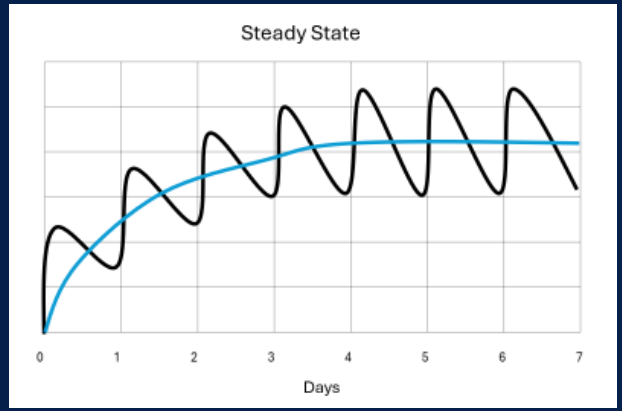



# Methadone Pharmacology

- Mu receptor agonist and NMDA antagonist
  - R and S- methadone enantiomers: R is more potent at mu while S is the NMDA antagonist
- Methadone affinity to mu receptor less than fentanyl
  - "Blocking dose"
- Dose stacking
  - Rapid titration of long-acting medications can lead to dose stacking

| Drug | $K_i$(nM) |
|---|---|
| Codeine | 734.2 |
| Oxycodone | 25.87 |
| Methadone | 3.37 |
| Fentanyl | 1.34 |



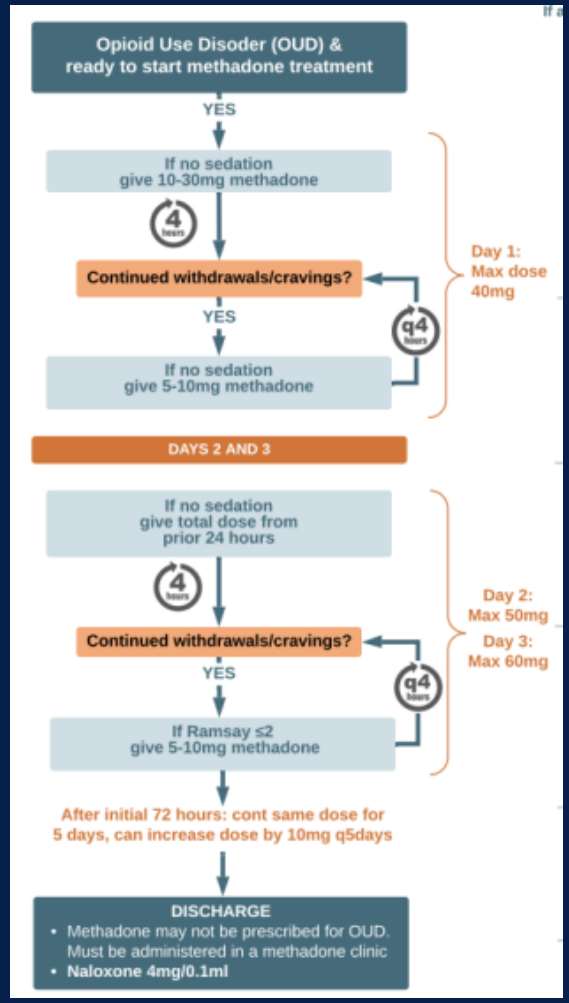




Volpe DA, McMahon Tobin GA, Mellon RD, Katki AG, Parker RJ, Colatsky T, Kropp TJ, Verbois SL. Uniform assessment and ranking of opioid μ receptor binding constants for selected opioid drugs. Regul Toxicol Pharmacol. 2011 Apr;59(3):385-90. doi: 10.1016/j.yrtph.2010.12.007. Epub 2011 Jan 6. PMID: 21215785.

# Standard Methadone Initiation Strategies

- Goals of starting methadone in the ED:
  - Relieving withdrawal symptoms and cravings
    - Decrease dose and frequency of fentanyl use

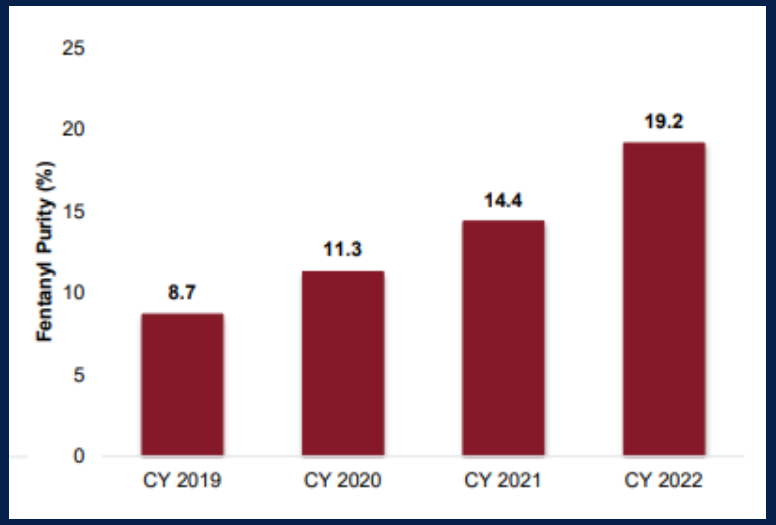
- Traditional hospital titration:
  - Start 10-30 mg PO daily
  - Reassess symptoms, may give 5-10 mg additional dose if needed.
  - Target stabilization in 5-7 days with gradual (~10 mg daily) increases



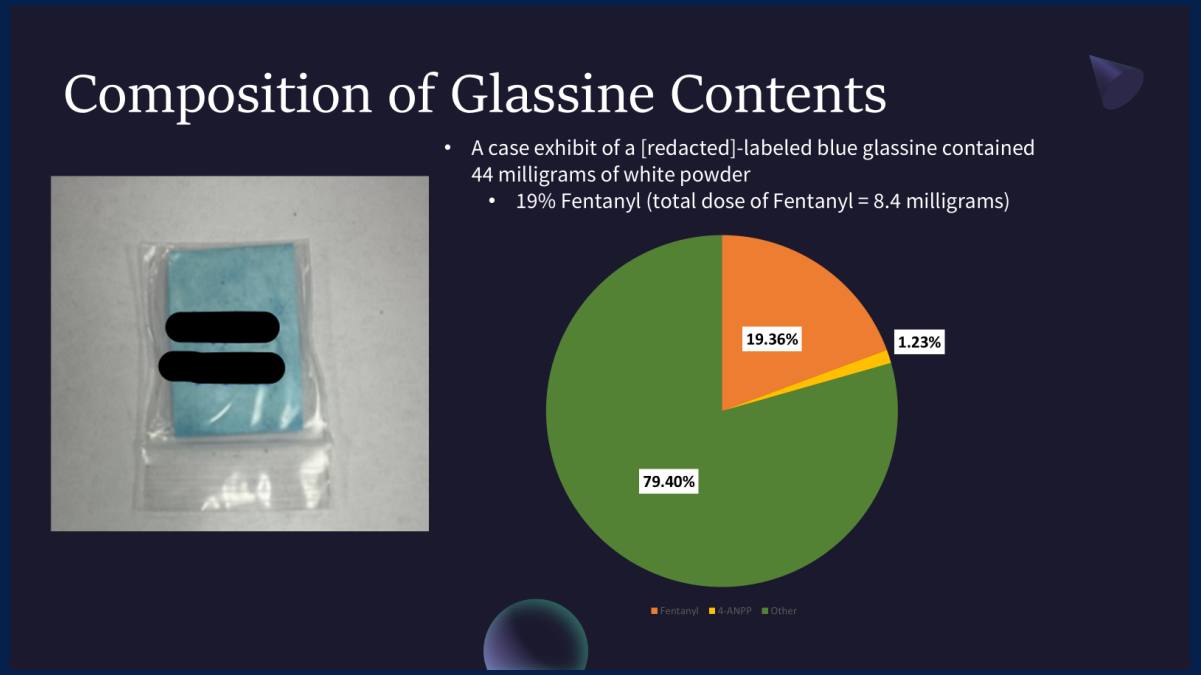

CA Bridge Methadone Hospital Quick Start

## **Purity and Adulterants/Diluents –** Powders and Tablets

- The average fentanyl purity was 19.2%. Fentanyl purity observed in FPP samples has increased consistently since CY 2019.
- The average tablet contained 2.4 mg of fentanyl with a range of 0.03 to 9.0 mg per tablet.




DEA: Fentanyl Profiling Program Reports CY2022
https://www.dea.gov/sites/default/files/2024-09/CY%202022%20FPP%20Report_PUBLIC_0.pdf



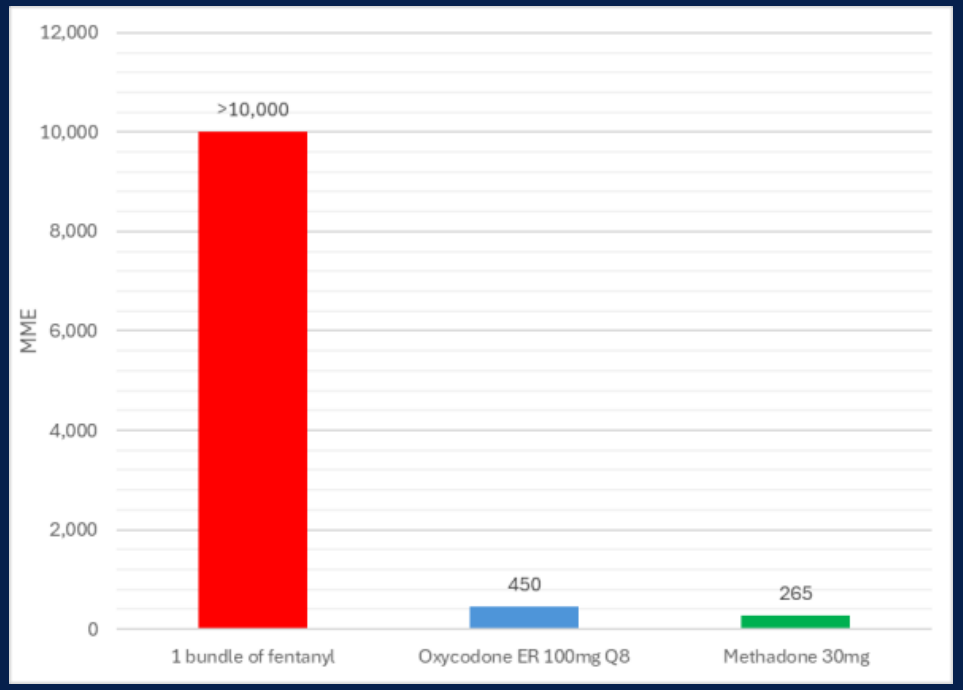

Credit: Ken Hand, MS. Laboratory Director, Cape May County Prosecutor's Office

# Methadone Initiation in the Fentanyl Era

- The dose of fentanyl in the community far exceeds the typical hospital therapeutic dose of opioid (50x or greater)

- A single bag of fentanyl in the Northeast often contains >5mg (600 MME)
- A single fentanyl pressed tablets commonly contains >2mg (240 MME)

- Methadone 30mg PO daily ~ 265 MME

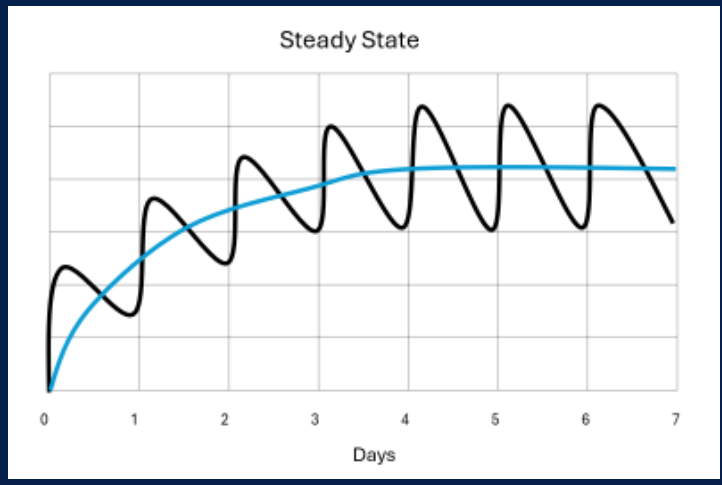



DEA: Fentanyl Profiling Program Reports CY2022
https://www.dea.gov/sites/default/files/2024-09/CY%202022%20FPP%20Report_PUBLIC_0.pdf

# Alternate Initiation Strategies

- Starting at higher initial doses:
  - Methadone 40 - 60mg PO daily

- Faster Titration of Methadone
  - Hospital-Based Rapid Methadone Initiation:
    - Methadone 40mg daily, followed by methadone 10 mg PRN withdrawal x 2-3 doses
      - Day 2: TDD from previous day, plus 10 mg PRN
      - Day 3: TDD from previous day, plus 10 mg PRN
  - Rapid Methadone Titration
    - Methadone 40, 60, 80mg on Day 1-3




- Low-Threshold/Harm-Reduction Model
  - Initial dose with post-discharge methadone take-home bottles (some states)

Liu P, Chan B, Sokolski E, Patten A, Englander H. Piloting a Hospital-Based Rapid Methadone Initiation Protocol for Fentanyl. J Addict Med. 2024 Jul-Aug 01;18(4):458-462. 2024 Jun 3.
Nikolaides JK, Tran TH, Ramsey E, Salib S, Swoboda H. A Novel Use of the "3-Day Rule": Post-discharge Methadone Dosing in the Emergency Department. West J Emerg Med. 2024 Jul;25(4):477-482.

# Alternative Routes of Administration

- Oral - Standard and preferred route
- Intramuscular (IM) or Intravenous (IV) Use
  - May be considered in hospital setting when unable to use oral route
  - 2:1 ratio for IV dosing (Oral 20mg = parenteral 10mg )


Hazekamp & Sacco, 2024, Emergency Medicine Practice

# Methadone & QTc Prolongation

- QTc prolongation is a significant risk when starting methadone.
  - Blockade of rapid delayed potassium rectifier and hERG channels
  - Methadone-associated torsade de pointes is a rare event (0.06 per 100 patient years)

- Risk Factors:
  - Induction phase
  - Doses >100 mg/day.
  - Electrolyte imbalances (K and Mg)
  - Slow metabolizers of methadone
  - Congenital long QT syndrome
  - Other QTc-prolonging meds (e.g., fluoroquinolones, SSRIs)
  - Structural heart disease
  - Female gender
  - Older age

- Management Strategies:
  - If QTc >450 ms, monitor more closely.
  - If QTc >500 ms, consider dose reduction under 100mg or switch to buprenorphine

Anchersen K, Clausen T, Gossop M, Hansteen V, Waal H. Prevalence and clinical relevance of corrected QT interval prolongation during methadone and buprenorphine treatment: a mortality assessment study. Addiction. 2009 Jun;104(6):993-9

# ECG Screening for Methadone

## 2009 ACP Recommendations:

- Clinicians should inform patients of arrhythmia risk when they prescribe methadone.
- Clinicians should ask patients about any history of structural heart disease, arrhythmia, and syncope.
- Obtain a pretreatment electrocardiogram for all patients to measure the QTc interval and a follow-up electrocardiogram within 30 days and annually. Additional electrocardiography is recommended if the methadone dosage exceeds 100 mg/d or if patients have unexplained syncope or seizures.
- If the QTc interval is greater than 450 ms but less than 500 ms, discuss the potential risks and benefits with patients and monitor them more frequently. If the QTc interval exceeds 500 ms, consider discontinuing or reducing the methadone dose; eliminating contributing factors, such as drugs that promote hypokalemia; or using an alternative therapy.
- Clinicians should be aware of interactions between methadone and other drugs that possess QT interval–prolonging properties or slow the elimination of methadone

Krantz MJ, Martin J, Stimmel B, Mehta D, Haigney MC. QTc interval screening in methadone treatment. Ann Intern Med. 2009 Mar 17;150(6):387-95

# ECG Screening for Methadone

**2020 ASAM National Practice Guidelines:**

- Patients should be informed of the potential risk of arrhythmia when they are dispensed methadone. It is recommended to get a history of structural heart disease, arrhythmia, or syncope.
- In addition, the clinician should assess the patient for other risk factors for QT-interval prolongation. An electrocardiogram (ECG) should be conducted for patients with significant risk factors including any prior ECG demonstrating a QTc >450 milliseconds, or a history suggestive of prior ventricular arrhythmia.
- ECG should also be considered when other risk factors for QT interval prolongation are present including when high doses of methadone are being employed, patient or family history of cardiac risk factors, abnormal liver enzymes, electrolyte abnormalities, or the patient is taking medications known to prolong the QT interval.
- While there are no clear data on the threshold dose of methadone that confers risk for QT interval prolongation, the consensus of the committee is that ECG should be considered for patients receiving over 120 mg per day. However, there is no research on the use of ECG data for improving patient outcomes

The ASAM NATIONAL PRACTICE GUIDELINE For the Treatment of Opioid Use Disorder 2020 Focused Update

# Managing Missed Doses in the ED

- Problems to consider:
  - Opioid tolerance - loss of tolerance leading to opioid toxicity upon restarting methadone
  - QTc prolongation associated with restarting methadone

- Variability in practice:
  - Uritsky & Casey, 2024
    - <3 days missed: Resume last stable dose
      - Stretch to 5 days?
    - ≥3 but <14 days missed: Restart at half dose, titrate up
    - ≥14 days missed: Restart as a new initiation

  - CA Bridge Methadone Quick Start 2023
    - If 1-2 days missed, administer the full dose.
    - If additional days missed, ask the clinic for recommended dosing.
      - Ex: 90% if 3 days missed, 80% if 4 days missed, 70% if 5 days missed, 60% if 6 days missed, 50% if 7 days missed, 40% if 8 days missed.

Uritsky & Casey, 2024, Journal of Opioid Management
CA BRIDGE Methadone Quick Start 2023

# Managing Missed Doses in the ED

## No Fentanyl Use

- Missed 1 – 4 days
  - *No dose adjustment*
- Missed 5 – 7 days AND Low Dose (less than 60 mg)
  - *No dose adjustment*
- Missed 5 – 7 days AND High Dose (60 mg or greater)
  - *Drop by 50% (but not lower than 40 mg)*
- Missed 8 or more days
  - *Restart at 40 mg*

## With Fentanyl Use

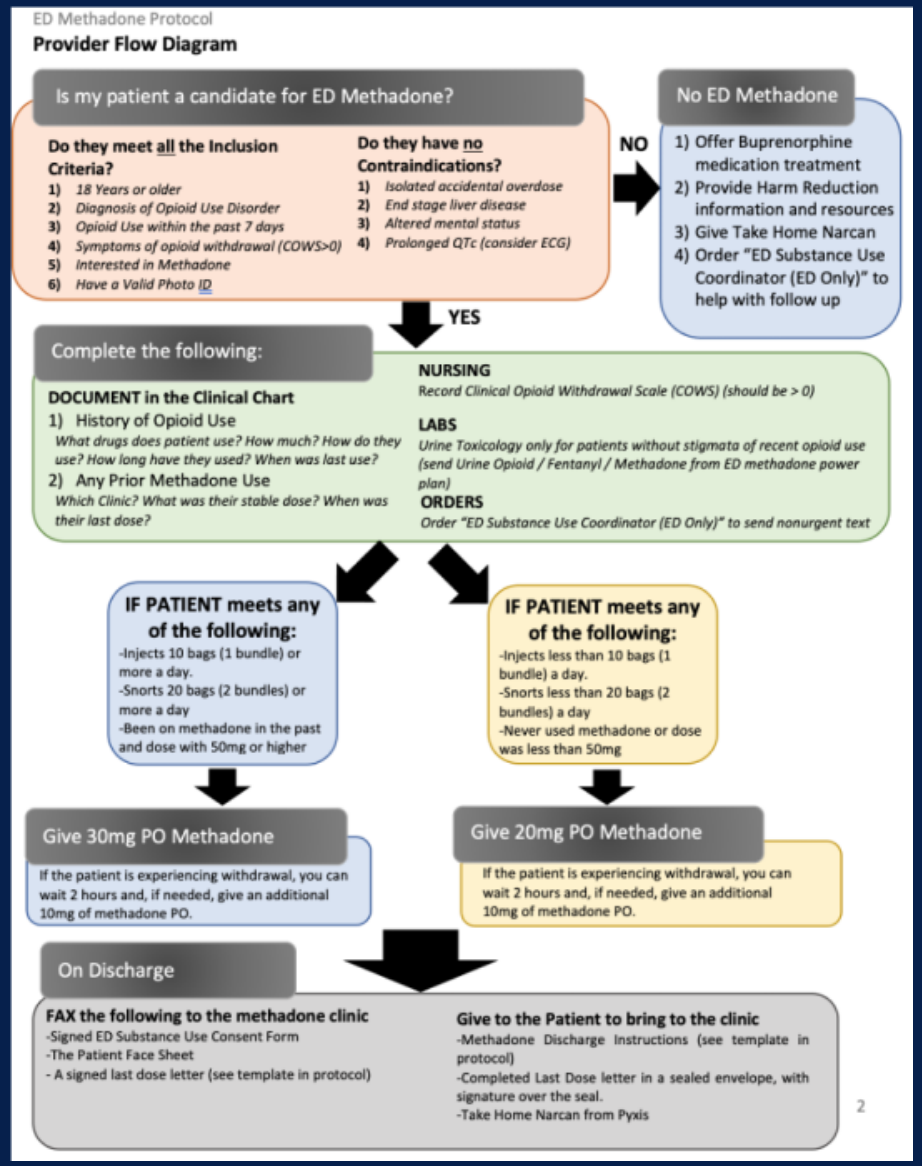
- Missed 1 – 4 days with fentanyl use
  - *No dose adjustment*
- Missed 5 or more days AND Methadone dose less than 60 mg
  - *No dose adjustment*
- Missed 5 or more days AND Methadone dose 60 mg or greater
  - *Decrease by 5 mg daily for each day missed after 4 days (but don't drop lower than 40 mg)*

Behavioral Health Network (BHN) Opioid Treatment Program Missed Dose Protocol, Western Massachusetts

# Process - Infrastructure and Leadership

- ED based Clinical Champion
- Partner OTP
- Stakeholder Acceptance
  - Clinical: ED Leadership / Nursing / Pharmacy
  - Non-Clinical: Legal / Compliance
- Policies and Protocols
  - Written Policies
  - Order Sets
- Education
- Feedback and Follow Up

# Process - Infrastructure and Leadership



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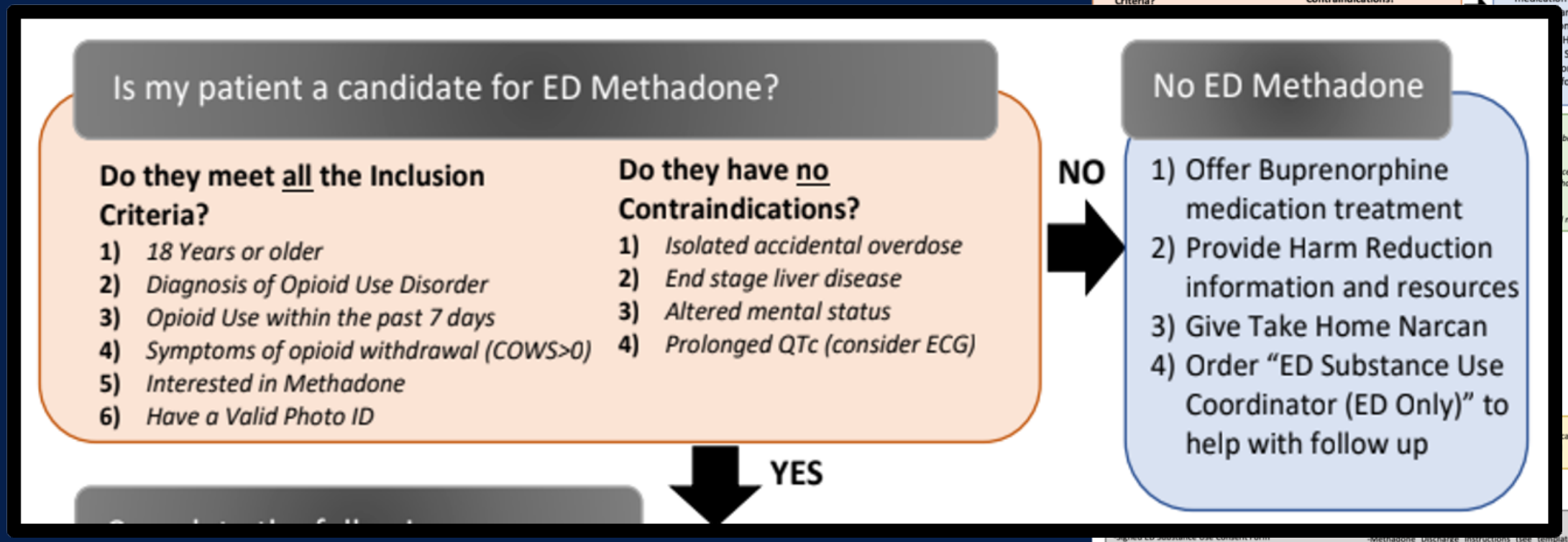

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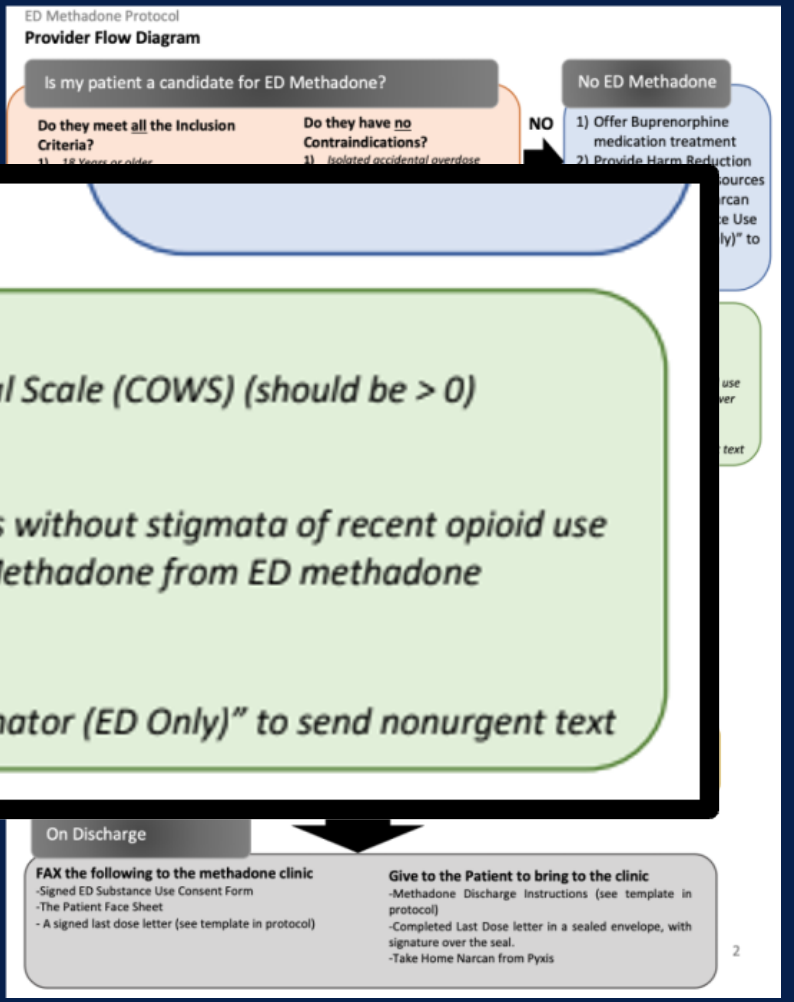

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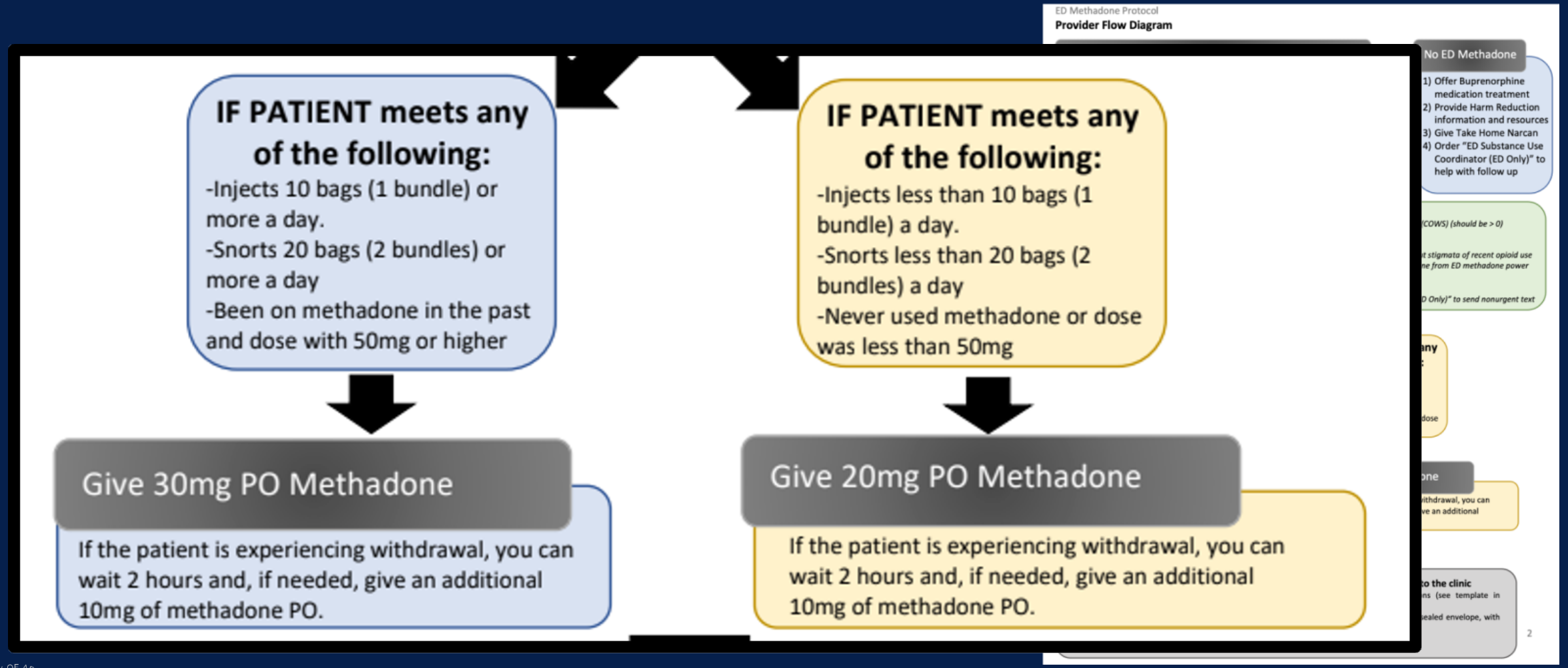

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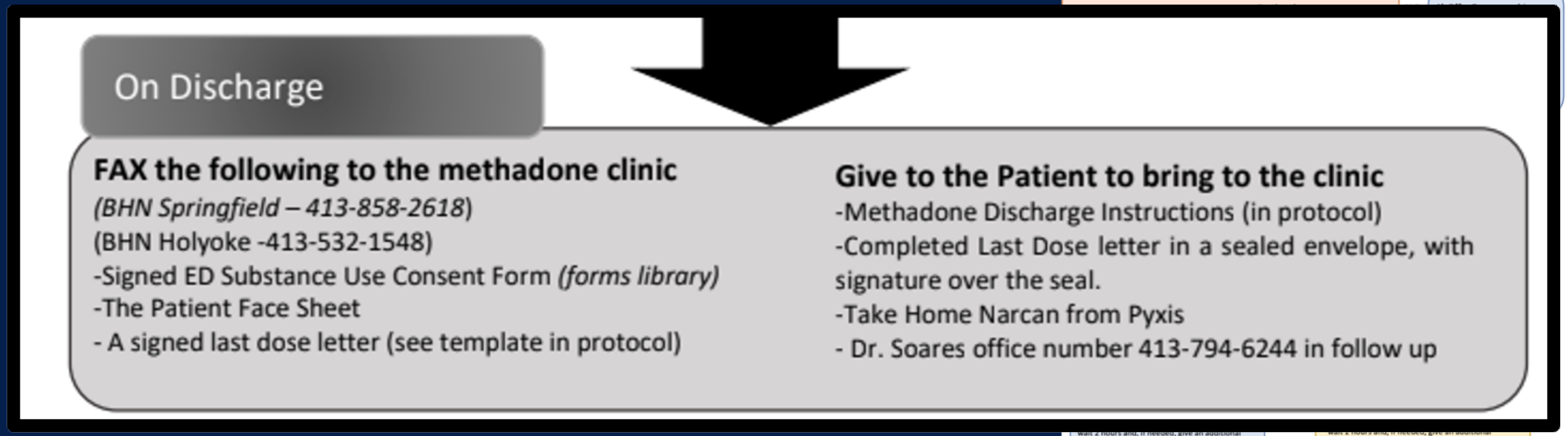

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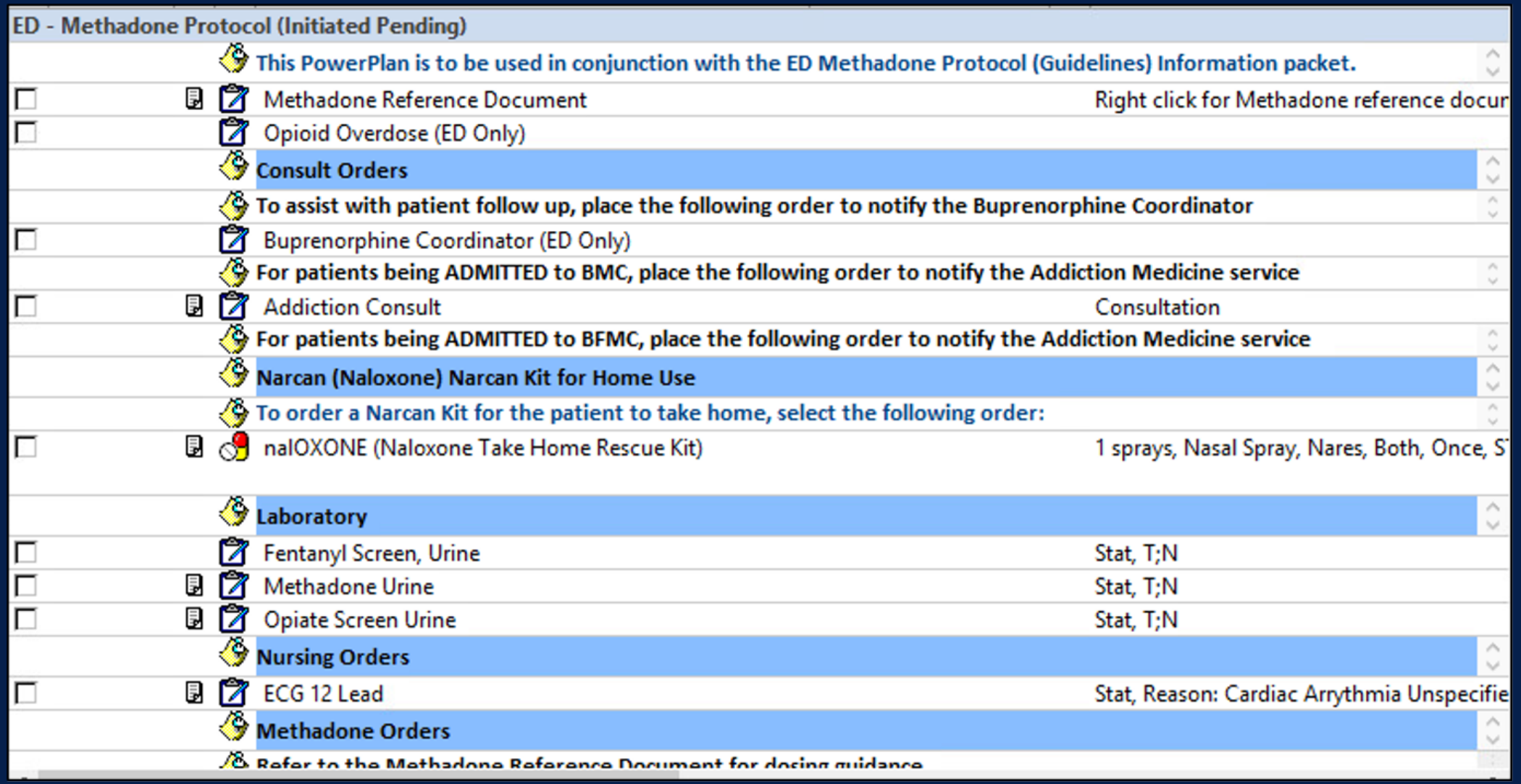

| ED - Methadone Protocol (Initiated Pending) | |
|---|---|
| This PowerPlan is to be used in conjunction with the ED Methadone Protocol (Guidelines) Information packet. | |
| Methadone Reference Document | Right click for Methadone reference docur |
| Opioid Overdose (ED Only) | |
| **Consult Orders** | |
| **To assist with patient follow up, place the following order to notify the Buprenorphine Coordinator** | |
| Buprenorphine Coordinator (ED Only) | |
| **For patients being ADMITTED to BMC, place the following order to notify the Addiction Medicine service** | |
| Addiction Consult | Consultation |
| **For patients being ADMITTED to BFMC, place the following order to notify the Addiction Medicine service** | |
| **Narcan (Naloxone) Narcan Kit for Home Use** | |
| To order a Narcan Kit for the patient to take home, select the following order: | |
| nalOXONE (Naloxone Take Home Rescue Kit) | 1 sprays, Nasal Spray, Nares, Both, Once, S |
| **Laboratory** | |
| Fentanyl Screen, Urine | Stat, T;N |
| Methadone Urine | Stat, T;N |
| Opiate Screen Urine | Stat, T;N |
| **Nursing Orders** | |
| ECG 12 Lead | Stat, Reason: Cardiac Arrythmia Unspecifie |
| **Methadone Orders** | |
| Refer to the Methadone Reference Document for dosing guidance | |

# Process - Infrastructure and Leadership

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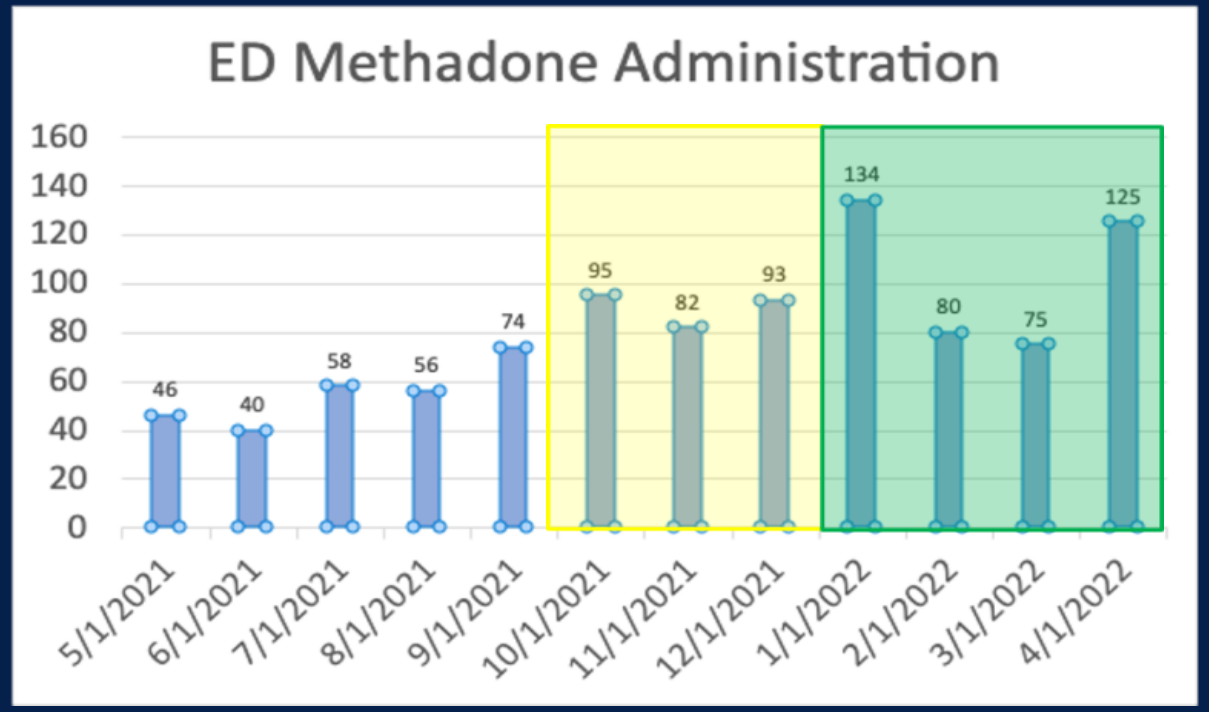


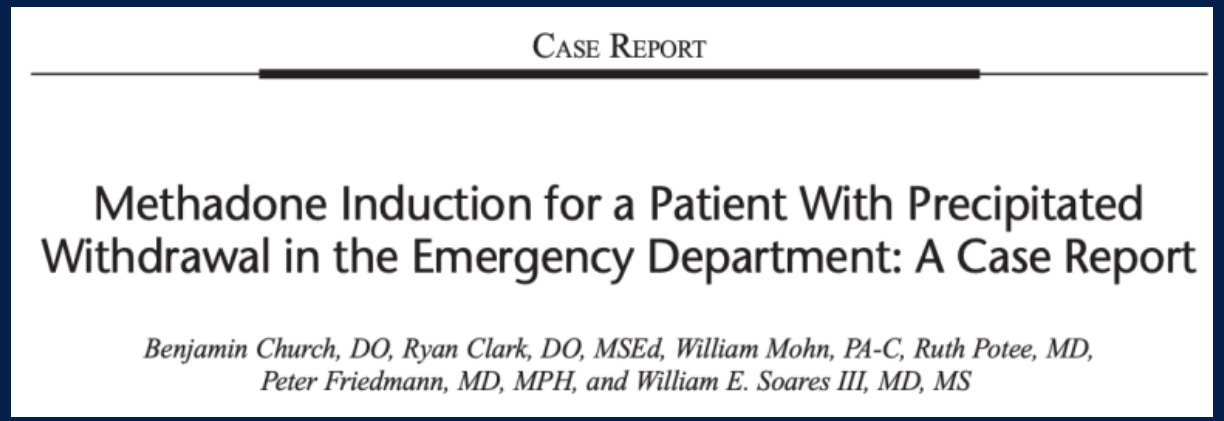

CASE REPORT

Methadone Induction for a Patient With Precipitated Withdrawal in the Emergency Department: A Case Report

*Benjamin Church, DO, Ryan Clark, DO, MSEd, William Mohn, PA-C, Ruth Potee, MD, Peter Friedmann, MD, MPH, and William E. Soares III, MD, MS*

Church B, Clark R, Mohn W, Potee R, Friedmann P, Soares WE 3rd. Methadone Induction for a Patient With Precipitated Withdrawal in the Emergency Department: A Case Report. J Addict Med. 2023;17(3):367-370.

# Case Presentations/Panel Discussion

We welcome your questions and comments!

1. New initiation of methadone
   - Simple start; high opioid requirements; not yet in withdrawal

1. Missed methadone dose (i.e., already engaged in an OTP)
   - Dose confirmed vs. unconfirmed

1. Engaging patients with MOUD reluctance

1. The “frequent flyer” on methadone

1. Acute pain in a patient on methadone maintenance

# Final Takeaways/Summary

Methadone plays a unique role in the fentanyl era

Methadone initiation and referral to an OTP from the ED is feasible from a regulatory and practical standpoint

Patient pathway differences may arise from geographic constraints and local regulatory impact

# QR Code for Clinical Toolkit

Referral algorithms

Dosing strategies and risk stratification

Literature/references

Guide to stakeholder recruitment and relationships

Tips of the Trade

# References


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Church B, Clark R, Mohn W, Potee R, Friedmann P, Soares WE 3rd. Methadone Induction for a Patient With Precipitated Withdrawal in the Emergency Department: A Case Report. J Addict Med. 2023;17(3):367-370.

# Case 1: Twisted Ankle

40 yo F presents to the ED with right ankle pain after apparently injuring it the night prior when she fell in the context of an overdose. She injects 1 bundle/day of fentanyl +/- cocaine. Last use 7 hours ago, after being reversed. She states withdrawal is coming on; COWS 2 for anxiety without objective signs of withdrawal. She reports having taken methadone 120mg for 6+ months until about 3 months ago because a patient at her OTP was "creeping on her." She becomes tearful describing how her life has fallen apart since stopping methadone. She refuses to even discuss buprenorphine, including whether she has ever tried it.

What do you do?

# Case 2: Missed Methadone

- 40-year-old male presents to the ED Saturday evening requesting methadone. He reports missing his Friday dose and weekend take-home doses because he was arrested for jumping a subway turnstile - (last dose ~ 60 hours ago). He states he gets 180mg/d at Happy Village OTP. He is sweating, restless, and just vomited in an emesis basin.

What do you do?

- What dose and how administered (oral/IM)?
- Confirm dose? When and what if not possible?

# Case: Incomplete Symptom Relief

Your patient who uses 2 bundles/day of IV  fentanyl presented with severe withdrawal.  You treated with methadone 10mg methadone IM twice.  Your hospital has a policy that precludes you from administering more than methadone 40mg oral equivalents. They are still quite ill with classic withdrawal.

What do you do?

# Other Cases We Might See

- 55-year-old man presents to the ED the 7th time seeking treatment for OUD in 6 months with or without other reasons for his visit.  He experienced buprenorphine precipitated withdrawal on his first visit. He was started on methadone on each subsequent visit but never/rarely followed-up at the OTP to which he as referred.

**What do you do?**