



# Medications for Opioid Use Disorder: Outpatient Clinical Considerations

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## Objectives

- Discuss the change in opioid epidemic with emergence of high-potency synthetic opioids
- Understand the difference between 3 medications to treat opioid use disorder and their clinical indications
- Learn initiation strategies for buprenorphine
- Identify precipitated withdrawal and ways to address patient discomfort
- Understand stabilization and long term treatment with buprenorphine

## Speaker Conflict of Interests

- Dr. Erin McKnight discloses no significant financial interests or relationships with commercial interests. The presentation will not include discussion of unapproved or “off-label” usage of commercial medications, products, or devices

## Opioid Epidemic

### *Synthetic Substances*

Illicit drug supply has likely permanently transitioned to synthetic substances – High Potency Synthetic Opioids, ie fentanyl and analogues<sup>1,2</sup>

Coincides with increased overdose deaths, other components in drug supply, high prevalence of polysubstance use<sup>2</sup>

Need to expand access to Medications for Opioid Use Disorder

## Fentanyl

- Very lipophilic
- Little dose needed for effect
- Stores in fat and accumulates
- When stopped, lingers in body and then starts to approximate methadone

Drug	Half life (distrib)	Half life (term)	LogP
Fentanyl	19 min	475 min	4.05
Morphine	68	548	0.89
Hydromorphone	60	1268	1.6
Methadone	120	1377	3.93

## Medication Treatment for Opioid Use Disorder

**GOLD STANDARD FOR TREATMENT OF OPIOID USE DISORDER**

## **MOUD as Standard of Care<sup>4</sup>**

- American Society of Addiction Medicine (ASAM)
  - Opioid withdrawal management (ie, detoxification) on its own, without ongoing treatment for opioid use disorder, is not a treatment method for opioid use disorder and is not recommended
- Substance Abuse and Mental Health Services Administration (SAMHSA)
  - Addiction is a chronic, treatable disease
  - The science demonstrating the effectiveness of medications for OUD is strong
  - It is not sound medical practice to deny people with OUD access to FDA-approved medications for their illness

## **Role of Medications in the Treatment of OUD<sup>4</sup>**

- Eliminates withdrawal
- Diminishes or eliminates drug craving and use of illicit opioids
- Blocks or attenuates the effects of fentanyl and other abused opioids
- Risk/harm reduction, reduces overdose risk
- Increased treatment retention and engagement in comprehensive rehabilitation
- Decreased medical and psychiatric symptoms, improves health, reduced risk of HIV and Hep C infection
- Improved social determinants such as employment, family relations
- Decreased criminal behavior

## OUD Treatment<sup>4</sup>

- Methadone
  - Full agonist
  
- Buprenorphine
  - Partial agonist
  
- Naltrexone
  - Full antagonist

## Methadone<sup>4</sup>

- Peak levels at 2-4 hrs, sustained x 24 hrs
- Half life 24-36 hrs, can range from 4-91 hrs
- Daily dosing, can divide for increased analgesia
- Benefits:
  - Analgesia, effective, structured environment, no risk of precipitated withdrawal
- Disadvantages:
  - Typical opioid side-effects: constipation, sedation, multiple drug-drug interactions, EKG changes at higher doses.
  - **Outpatient treatment via Opioid Treatment Program (OTP)**
    - Usually requires daily visits for dosing
    - Cannot be prescribed at hospital discharge
    - Can pose difficulties with discharge planning

## Buprenorphine<sup>4</sup>

- Onset of action 30-60 min
- Peak effect 90-100 min, half-life 24-42 hrs
- Daily or BID oral dosing (most frequently)
  - monthly injection available
- Benefits:
  - Likely ceiling effect to sedation / respiratory depression
  - More options for therapy compared to methadone
  - Allows treatment of co-morbid pain
- Disadvantages:
  - Can precipitate withdrawal, requires fentanyl washout period (2-5 days)
  - Can alter LFTS, consider dose reduction or transition to mono form if >3x upper limit of normal, coagulopathy

## Recent Buprenorphine Changes

- Practice Guidelines for the Administration of Buprenorphine for Treating Opioid Use Disorder
  - X waver training requirement is waived
  - Need to have valid license and DEA
  - Applies to MD/DO/NP/PA
  - Notice of Intent (waiver) no longer required

## **For a New or Renewed DEA Registrant:**

- One of the following:
  - A total of eight hours of training from certain organizations on opioid or other substance use disorders for practitioners renewing or newly applying for a registration from the DEA to prescribe any Schedule II-V controlled medications;
  - Board certification in addiction medicine or addiction psychiatry from the American Board of Medical Specialties, American Board of Addiction Medicine, or the American Osteopathic Association; or
  - Graduation within five years and status in good standing from medical, advanced practice nursing, or physician assistant school in the United States that included successful completion of an opioid or other substance use disorder curriculum of at least eight hours.

## **Treatment of OUD with Buprenorphine**

- Despite research showing benefits for treatment of OUD, resistance remains
- Briefly will touch on current treatment
- Recent research regarding buprenorphine initiation
  - High dose initiation (macro dosing)
  - Low dose initiation with continuation of opioid agonist (micro dosing)

## **Standard Initiation<sup>3</sup>**

- Most well described, previously used with heroin, prescription opioids
- Need to be in moderate opioid withdrawal to start
  - use adjuvant medications to help withdrawal
- Initial dose – 2-8 mg
- Duration of initiation until stable, 1-3 days
- No full agonist continuation
- Moderate care coordination required

## **Standard Initiation<sup>5</sup>**

Any treatment setting

Daily Dosing Strategy

1 – 2-4 mg starting dose, up to 8-12 mg

2 – 4-16 mg

3 – 4-24 mg



## Precipitated Withdrawal and Fentanyl<sup>6</sup>

- Fentanyl lipophilic and has distribution to peripheral tissues that is not dose dependent
- Continuous and prolonged use of fentanyl can result in increased volume of distribution systemically with slow dissipation overall
- Standard practice much more likely to precipitate withdrawal than in the past

## Precipitated Withdrawal

- Precipitated withdrawal during buprenorphine initiation can be a barrier to successful initiation and stabilization<sup>2</sup>
- Buprenorphine has higher affinity for the  $\mu$  receptor. If given, when most of receptors still occupied by a full agonist, it will displace the full agonist causing withdrawal symptoms<sup>2</sup>
- Need to discuss expectations, setting for initiation, and what treatment for precipitated withdrawal will be before start initiation<sup>7</sup>

## Precipitated Withdrawal

- Most effective treatment is to give more buprenorphine
  - Improvements in symptoms with rapid escalation to 24-32 mg on day of initiation<sup>8</sup>
- As more  $\mu$  opioid receptors are bound with buprenorphine, agonism is optimized<sup>8</sup>
- Use alpha-2 agonists, symptom directed adjunctive medication
- Intractable withdrawal that does not respond to above interventions requires hospital-level interventions<sup>3</sup>

## High Dose Buprenorphine<sup>3</sup>

- Quick stabilization
- Need to be in at least mild withdrawal (COWS >8)
- Initial starting dose 8-16+mg, escalate rapidly to 16-32 mg in 1-2 doses
- Duration of initiation until stabilization - <2 h
- No need for opioid continuation
- Moderate care coordination required
- Outpatient\*, ED, Urgent Care

## High Dose Buprenorphine Initiation

- Increasing initial dose > 8 mg results in increasing agonist  $\mu$  receptor activation and strengthening opioid blockade
- Prospective cohort of ED patients with fentanyl use had precipitated withdrawal <1% after receiving initial buprenorphine dose of  $\geq 8$  mg<sup>9</sup>
- 2 retrospective cohort studies showed no increased adverse events compared with standard initiation<sup>10</sup>

## High Dose Buprenorphine Initiation<sup>11</sup>

- Any treatment setting
- Daily Dosing Strategy
  - 1 – 8-24 mg initial dose
    - Doses of 8-24 mg can be administered every 30-60 minutes with initial observation
  - 1,2 -  $\geq 24$  mg

## **Low Dose Buprenorphine Initiation with Opioid Continuation**

- Patient's use full agonist opioid during multiday dose escalation of low-dose buprenorphine<sup>12</sup>
- Continuing full agonist maintains the level of  $\mu$  opioid receptor activation needed to match a patient's baseline opioid tolerance
- In hospital setting or ED setting, can prescribe full agonist opioid for protocol
- In outpatient setting, not able to prescribe full agonist opioid for treating OUD (federal law)
  - Can prescribe full agonist to OUD patients with pain
  - Have patient use their own non-prescribed opioid during buprenorphine dose escalation

## **Low Dose Buprenorphine Initiation with Opioid Continuation<sup>3</sup>**

- Variety of dosing strategies to use
- No specific dosing schedule for either full agonist opioid or buprenorphine has been determined
- Most cases occur in hospital setting
- Best for patients with pain transitioning from full agonist to buprenorphine, patients admitted to hospital, and patients enrolled in OTP transitioning from methadone to buprenorphine

## Buprenorphine Stabilization

- No longer experience withdrawal and have minimal to no opioid cravings<sup>13</sup>
- Long term treatment after stabilization is recommended as long as the patient benefits – can be for a lifetime
- Individuals that use synthetic opioids may have more difficulty achieving stabilization and require higher doses of 24-32 mg daily<sup>3</sup>

## Buprenorphine Stabilization

- Extended release buprenorphine (depo formulation) is option for those who struggle to stabilize
  - Also helpful for patients who want decreased visits, concern for diversion, greater ability to adhere to treatment
- 2 formulations – Sublocade<sup>®</sup> and Brixadi<sup>®</sup>
  - At highest doses, Sublocade achieves similar or higher buprenorphine plasma levels compared to 24 mg daily buprenorphine<sup>14</sup>
- Compared with sublingual buprenorphine, XR has shown reductions in opioid use and overdose<sup>15</sup>

## Other MOUD?

- Medications for treating OUD should be available to all patients – methadone, buprenorphine, naltrexone
- When choosing, consider patient's preference, past treatment history, current state of illness
- Many may prefer buprenorphine, but repeated unsuccessful initiation and stabilization attempts may require other MOUD options<sup>3</sup>
  - Methadone is first line treatment alternative, need to go to OTP

## Naltrexone

- Initiation challenging for those with extensive fentanyl use due to prolonged elimination, requires longer opioid free interval to start<sup>16</sup>
- Higher risk of overdose when stop using<sup>22</sup>
- Individuals using fentanyl less likely to initiate XR Naltrexone than buprenorphine or methadone<sup>21</sup>
- If patient is highly motivated, consider rapid conversion in a controlled environment<sup>17</sup>

## In addition to MOUD

- Always prescribe naloxone and reassess if need more
- Consider fentanyl test strips
  - Best for people who are buying pills, concerned if laced



## Medications for Opioid Use Disorder: Inpatient Clinical Considerations

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## **Objectives**

- Acknowledge the need for inpatient initiation of buprenorphine
- Describe various low dose buprenorphine initiation strategies
- Understand use of high dose buprenorphine initiation protocol in inpatient setting
- Discuss use of methadone as an alternative

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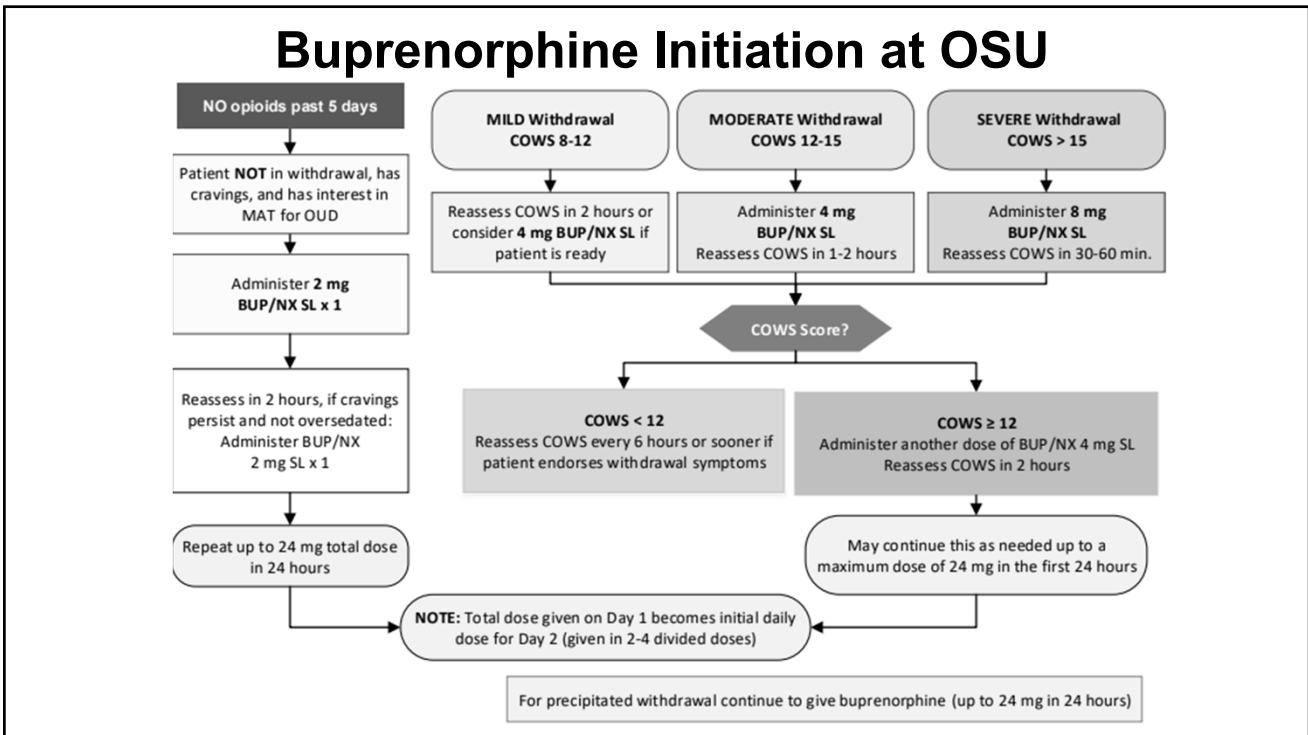
## **Inpatient initiation considerations**

- Patients admitted for medical complications and concurring opioid withdrawal
  - Can be helpful to keep patient adherent to inpatient stay if manage OUD
- Patients with opioid use disorder, on full agonist for pain control, wanting to transition to MOUD
- Patients wanting to initiate inpatient treatment of MOUD

## **OUD Treatment (OSU Guidelines Overview)**

- Screen patients for potential OUD
- Check OARRS (Ohio Automated Rx Reporting System)
- Document opioid use
  - Which opioids, frequency, duration, last dose
- Lab work
  - Urine toxicology, LFTs, urine pregnancy, HIV, STI, Hep B/C
- Obtain a Clinical Opiate Withdrawal Scale (COWS) score
- Consider adjunctive medications for symptom control

Medication	Dose	Indications
Acetaminophen	650 - 975 mg PO every 6 hours as needed based on liver function	Myalgia, bone pain
Ibuprofen (contraindicated in pregnancy)	400 mg PO every 6 hours as needed	Myalgia, bone pain
Clonidine	0.1 mg PO every 6 hours as needed Not to exceed 1.2 mg/24 hours, hold if BP < 100/70 mmHg Requires tapering before discontinuation if used regularly	Withdrawal symptoms (tachycardia, hypertension, hyperthermia), diaphoresis, lacrimation, rhinorrhea, piloerection, mydriasis, yawning)
Ropinirole	0.25 – 0.5 mg PO every 6 hours as needed	Restless leg syndrome
Gabapentin (in-hospital use only)	100 mg PO TID <i>or</i> 300 mg every HS	Restless leg syndrome
Hydroxyzine	25 - 50 mg PO every 8 hours as needed	Anxiety
Loperamide	4 mg PO x 1 initially, then 2 mg 4 times daily as needed Not to exceed 16 mg/24 hours	Diarrhea
Dicyclomine	10 – 20 mg PO every 6 hours as needed	Abdominal cramping
Ondansetron	4 – 8 mg PO every 6 hours as needed	Nausea and vomiting
Melatonin	3 – 6 mg every night as needed	Insomnia
Trazodone	50 mg every night as needed	Insomnia
Lorazepam	1 – 2 mg IV/IM/PO once and monitor	Precipitated withdrawal



## Sample Case 1

- Patient X is a 36-year-old who originally was introduced to opioids through a prescription for acute pain and has since continued to use increasing doses of prescription opioids, going to various providers for medication and taking them from a family member with a chronic pain condition. They have presented to the hospital with fevers and chills. They state that their last use of opioid was about 12 hours ago.
- Upon admission they seem very uncomfortable. You discuss with them your concerns about their fevers, but before you are done with the interview they ask how long their stay will be and when they can leave.
- A COWS is obtained and is 21

## Sample Case 1 (cont)

- Possible next steps
  - Try to get them through this admission with symptom control
  - Treat their withdrawal with standard opioids
  - Discuss with the patient if they would like to start treatment for their OUD with buprenorphine/naloxone (BUP/NX)
    - They agree and are given 8mg SL dose and symptoms of withdrawal significantly improve on repeat COWS
    - Social work meets with patient to discuss discharge planning and OUD treatment follow-up

## Sample Case 2

- Our same patient X is presenting for the same problem, but this time instead of having used prescription opioids they have been buying their opioids off the street “because they are cheaper” and don’t have any where else to get them
- They again last used 12 hours ago and again are uncomfortable and exhibiting signs of withdrawal on admission.
- You again discuss with them your recommendations and they accept the 8mg dose of BUP/NX, but this time things get worse. COWS shoots up and they look even more miserable.
- What happened?

## Sample Case 2

- Most opioids bought in current drug market are fentanyl or laced with fentanyl – always assume fentanyl
- Patient thinks they are buying an oral prescription opioid, but are getting a pressed pill
  - Very little “true” Percocet, Oxycodone, Vicodin
- Make sure urine drug screen identifies fentanyl vs other opioids – not seen in point of care urine drug screens, need GC/MS
  - Look for fentanyl or metabolite norfentanyl

## Introduction to Microdosing

- Our group and many others encountered problems with standard induction and precipitated withdrawal
  - Patients were hesitant due to previous precipitated withdrawal (street buprenorphine or even in house)
  - Patients were on full agonists for pain
  - Patients wanted to switch from methadone to BUP/NX
  - Patients were fentanyl users and at higher risk for precipitated withdrawal.

## The Bernese Method

- Dr Hämmig of Bern University in 2010 noted some of their patients would experience withdrawal with standard induction
- Also noted
  - Some patients on BUP use full opioid agonist without negative effect
  - Effects of antagonists is reduced with repetitive small doses
- Proposed the 'Bernese method' ('Berner Methode')
  - Start with 0.2mg of BUP WITHOUT stopping full agonist
  - Slowly increase the dose day by day
  - At sufficient dose, stop full agonist

## Inpatient Low Dose Initiation

- Buprenorphine formulation
  - Sublingual
  - Transdermal patch
  - Buccal
- Full Agonist

## Low Dose Buprenorphine Initiation Rapid Approach<sup>18</sup>

Day	Buprenorphine Dose	Full Agonist Opioid Dose*
1	Buprenorphine 0.5 mg SL every 3 hrs	Oxycodone IR 15-20 mg PO every 3-4 hrs
2	Buprenorphine 1 mg SL every 3 hrs	Oxycodone IR 15-20 mg PO every 3-4 hrs
3	Buprenorphine 8-16 mg SL and additional as needed	Oxycodone IR 15-20 mg PO every 3-4 hrs, STOP at end of day

\* Choice of full agonist depends on patient opioid tolerance, underlying pain condition, and clinical evaluation. Can also use Methadone 40-50 mg qday

## Low Dose Buprenorphine Initiation Rapid Approach<sup>19</sup>

Day	Buprenorphine Dose	Full Agonist
1	Buprenorphine 20 mcg/hr transdermal patch	Oxycodone IR 15-20 mg PO q 3-4 h
2	Buprenorphine 1 mg SL q 3 h	Oxycodone IR 15-20 mg PO q 3-4 h
3	Buprenorphine 1 mg SL q 3 h (8am-11 pm)	Oxycodone IR 15-20 mg PO q 3-4 h
4	Buprenorphine 1 mg SL at 6 AM, followed by 8 mg SL at 9 am	Continue full agonist as needed

## Slower Approach<sup>20</sup>

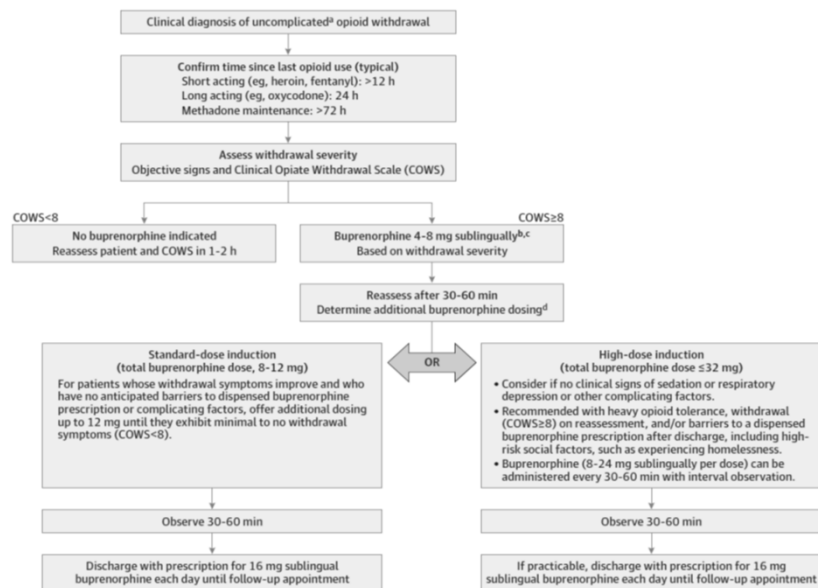
Day	Buprenorphine Dose	Full Agonist
1	Buccal Buprenorphine 225 mcg once	Oxycodone IR 15-20 mg PO q3-4 hr
2	Buccal Buprenorphine 225 mcg BID	Same full agonist
3	Buccal Buprenorphine 450 mcg BID	Same full agonist
4	Buprenorphine/naloxone 2 mg SL BID	Same full agonist
5	Buprenorphine/naloxone 4 mg SL BID	Same full agonist
6	Buprenorphine/naloxone 4 mg SL TID	Same full agonist
7	Buprenorphine/naloxone 8mg SL BID	STOP
8	Buprenorphine/naloxone 8 mg SL BID-TID	

## Slower Approach<sup>21</sup>

Day	Buprenorphine Dose	Full Agonist
1	Buprenorphine/naloxone 0.5 mg SL qday	Oxycodone IR 15-20 mg PO q3-4 h
2	Buprenorphine/naloxone 0.5 mg SL BID	Same full agonist dose
3	Buprenorphine/naloxone 1 mg SL BID	Same full agonist dose
4	Buprenorphine/naloxone 2 mg SL BID	Same full agonist dose
5	Buprenorphine/naloxone 4 mgSL BID	Same full agonist dose
6	Buprenorphine/naloxone 4 mg SL TID	Same full agonist dose
7	Buprenorphine/naloxone 8 mg SL BID	STOP
8	Buprenorphine/naloxone 8 mg SL BID-TID	

## Inpatient High Dose Protocol

Figure 1. High-Dose Buprenorphine Treatment Pathway





## Methadone Induction<sup>22</sup>

- First alternative for individuals adverse to buprenorphine
- Patients with fentanyl exposure may need closer monitoring, use of adjunctive medications, faster up titration of methadone
- Access after discharge (OTP) complicates post hospital treatment

## Methadone Induction

Table 1: Alternate MAT Agents with Limited Use

Medication	Contraindications	Considerations
Methadone	<ul style="list-style-type: none"> <li>• <b>Relative contraindications:</b> morbid obesity, OSA, obesity hypoventilation syndrome, severe COPD, ongoing use of sedatives, regular alcohol use, precipitated withdrawal if not tapered off at higher doses</li> <li>• <b>Absolute contraindications:</b> allergy, acute liver failure</li> </ul>	<ul style="list-style-type: none"> <li>• <b>Cannot be prescribed for OUD at discharge.</b> Patient must have a next day appointment at a federally sanctioned Opioid Treatment Program (OTP). Only a few of these exist in Columbus and often require assessment appointments prior to starting methadone therapy. Initially, patients must wait in line <u>every day</u> for their dose.</li> <li>• Slow onset, long half-life (up to 3 days), and greater risk of opioid toxicity.</li> <li>• Can start immediately without concern for precipitating withdrawal: 20-30 mg daily. Titrate slowly as it can take a few days to reach steady state levels.               <ul style="list-style-type: none"> <li>○ Cannot prescribe methadone for OUD at discharge</li> <li>○ Will need next day appointment at OTP if this is the treatment plan chosen</li> <li>○ Unlikely to require taper due to low dose</li> </ul> </li> </ul>

## Odds and Ends

- Consider if medications requires a prior authorization
- Have good communication with inpatient pharmacy team
- Prescribe patients intranasal naloxone
- Set up every new patient with an appointment for outpatient fu within 7 days – utilize social work

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