

Inpatient Management of Opioid Use Disorder: Buprenorphine

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Disclaimer:

These clinical practice guidelines do not set a standard of care, rather they are an educational aid to practice. They do not set a single best course of management, nor do they include all available management options. They were developed by an interdisciplinary team based on published evidence and expert opinion; as the literature develops best practices may change. They should never be used as a substitute for clinical judgement. Individual providers are responsible for assessing the unique circumstances and needs of each case. Adherence to these guidelines will not ensure successful treatment in every situation. This information is intended for healthcare providers and subject matter experts, it is not intended for use by patients and the general population.

This guideline applies to patients in inpatient medical settings. If any of the following points are different for pregnant patients, it is noted in each segment of the following document.

Goal of Treatment:

- COWS (Clinical Opioid Withdrawal Score – See Appendix A) of 5 or less for 24-36 hours
- Elimination of drug hunger or cravings
- No sedation or respiratory depression from medication
- If patient uses illicit opioids while on buprenorphine, they should not feel substantially intoxicated

Monitoring:

- COWS score is used to monitor a patient's response to buprenorphine, it can be done by a provider or RN
- COWS assessments during induction should be done per protocol (See Appendix B), generally 1 hour after the first medication dose and q 6 hours while the patient is awake.
- Standing COWS can be discontinued when the dose is stabilized, when COWS is < 5 over at least 24 hours, or automatically stopped after 72 hours.
- **Pregnancy Only:** Fetal monitoring beyond what is necessary for initial fetal evaluation is not necessary solely for methadone administration unless ordered by the provider.

Patients on outpatient buprenorphine or buprenorphine-naloxone:

- 1) Confirm dose by calling their pharmacy or checking the PDMP (in California this is <https://cures.doj.ca.gov>).
- 2) Unless patient has a severe alteration in mental status or other contraindication (including missed doses as below), provider will continue patient's outpatient dose by writing a medication order. COWS is not necessary.
- 3) Buprenorphine should typically be continued during acutely painful events, but buprenorphine alone will not control severe acute pain—see separate acute pain guidelines.
- 4) If patient has missed outpatient dosing and has not used opioid agonists in the interim, provider may order patient's full outpatient dose.
- 5) If patient has missed >1 day of buprenorphine AND has use opioid agonists in the interim, use clinical judgement to determine whether they are at risk for precipitated withdrawal. If, based on their period of time without buprenorphine, opioid use, and lack of current objective withdrawal you are concerned for precipitated withdrawal, please consider them a new induction and follow protocols in Appendix B.

Patients considering buprenorphine induction:

1. Determine clinical indication for buprenorphine therapy:

<u>Indication</u>	<u>Contraindications</u>	<u>Caution</u>
<ul style="list-style-type: none"><input type="checkbox"/> Opioid use disorder, with or without comorbid chronic pain <p><u>and</u></p> <ul style="list-style-type: none"><input type="checkbox"/> Desire for buprenorphine treatment to assist with cessation or reduction in use	<ul style="list-style-type: none"><input type="checkbox"/> Allergy to buprenorphine<input type="checkbox"/> Medically unstable and unable to tolerate mild withdrawal safely	<ul style="list-style-type: none"><input type="checkbox"/> Severe psychiatric illness that limits ability to take daily medication, mania<input type="checkbox"/> Acute pain requiring opioid agonist therapy or anticipated surgery in next 48 hours<input type="checkbox"/> EtOH or benzodiazepine use disorder<input type="checkbox"/> Liver disease<input type="checkbox"/> Use of methadone in the last week<input type="checkbox"/> Pregnancy only: induction may occur at outpatient clinic or inpatient under obstetric team guidance <p>If the patient falls under the “caution” category, call the UCSF Substance Use Warmline (855.300.3595 or https://tinyurl.com/yd4ymyx6) or your local addiction specialists.</p>

2. Discuss options with patient and determine whether methadone or buprenorphine would be preferable (See Appendix C – Non-pregnancy Decision Guide; **Pregnancy Only:** See Appendix D – Pregnancy Only Decision guide). In the inpatient setting clinicians can legally order buprenorphine or methadone if the patient is admitted primarily for another medical reason, regardless of if they have an X license/DATA 2000 waiver. Additionally, prior to starting buprenorphine, ensure that someone in your hospital will be able to write a short prescription on discharge and that there are providers in the patient’s area who are willing to prescribe buprenorphine after discharge for maintenance therapy.

3. Prior to induction:

- Verify DSM 5 criteria for opioid use disorder
- Check baseline LFTs (rarely can cause hepatotoxicity), urine pregnancy test, check urine tox and CURES report for collateral information about substance use

Pregnancy Only: also check baseline maternal vital signs, NST or fetal heart tones as indicated, and a urine tox (utox can only be performed after patient verbal consent)

- If a patient is experiencing mixed alcohol and opioid withdrawal, be very cautious and consult with experts to determine which pathology predominate as the combination of benzodiazepines and opioids can be high risk
- Follow the attached flow sheet (appendix B) to ensure that the patient does not have fully activated opioid receptors, as this can lead to precipitated withdrawal from buprenorphine (very uncomfortable).

Pregnancy only: precipitated withdrawal can cause withdrawal symptoms in the fetus. Precipitated withdrawal is unlikely to occur if one of the following is true:

- COWS score ≥ 8 with some objective signs of opioid withdrawal
- Patient who has been abstinent for a prolonged period, usually weeks (eg recently incarcerated, prolonged hospitalization without opioids)
- Consider adjunctive medications to help to control withdrawal symptoms, prior to starting and during induction. Check for contraindications and drug-drug interactions before beginning any new medications. Of note, this will lower COWS scores therefore may prolong the induction.
 - Acetaminophen 650 mg PO 6 four times daily PRN pain
 - Clonidine 0.1 -0.3 mg PO q6-8 hours prn w/d symptoms (NTE 1.2 mg/24 hours, hold if BP<100/70)
 - Diphenhydramine 25-50 mg, PO three times daily prn insomnia/anxiety
 - Ibuprofen 400-800 mg, PO four times daily prn pain (**Pregnancy Only:** *Ibuprofen is contraindicated*)
 - Loperamide 4 mg PO x 1 initially, then 2 mg prn each additional loose stool (NTE 16 mg/24 hours)
 - Ondansetron 4 mg PO every 6 hours PRN nausea
 - Melatonin 3 mg qHS PRN insomnia
 - Trazodone 50 mg qHS PRN insomnia
 - DO NOT ORDER benzodiazepines as standard PRN adjunctive therapy.

4. Follow attached algorithm for dosing. Follow algorithm in Appendix B for dosing. Provider or RN trained in evaluation must evaluate via COWS per protocol. The total dose on the first day should not exceed 16 mg. On day two, start with day one's total daily dose and give additional doses as needed per the algorithm. If precipitated withdrawal is suspected at any point, or if withdrawal symptoms are uncontrolled on the maximum daily dose, call the Substance Use Warmline (see below) or your local addiction specialist. Management usually involves repeating buprenorphine dose, adjunctive medications, or if patient is unstable, giving full opioid agonist with strong affinity.

Discharge Planning

- 1) Call local buprenorphine prescriber (see SAMHSA database at <https://tinyurl.com/mtyjtm5>) to arrange appointment for patient after discharge. Ideally, this appointment will be within 3 days of discharge.
- 2) On discharge, provide enough buprenorphine to last until appointment at outpatient clinic. Of note, depending on pharmacy formularies inpatients may receive buprenorphine alone (Subutex), however

buprenorphine-naloxone (Suboxone) should be dispensed on discharge to discourage diversion. Medi-Cal covers buprenorphine and buprenorphine-naloxone, with some other insurance providers a TAR may be necessary. Discharge prescription must be written by X licensed provider.

- 3) If no X licensed provider is available to write a discharge prescription, one of the following should occur:
 - a. Appointment with X waived provider the day after discharge.
 - b. Return to ED or for administration (not prescription) of buprenorphine, which is legal for up to 72 hours.
 - c. Consider a loading dose on day of discharge of up to 32 mg--this may prevent withdrawal for up to 72 hours, without clinically significant sedation or respiratory depression.
- 4) Skilled nursing facilities (SNFs) that are not classified as hospitals can only keep patients on buprenorphine if they have an outside provider—discuss these details with the SNF early in the process.
- 5) Please prescribe naloxone in case of relapse and overdose, also consider PREP/PEP if indicated.

Other Dosing Considerations

- Product Selection:
 - The standard approach is to use sublingual films or tablets for treatment of opioid use disorder.
 - In the hospital, either buprenorphine monoproduct or combination buprenorphine-naloxone may be used.
 - On discharge, the combination buprenorphine-naloxone is recommended due to decreased diversion and does not have increased rates of side effects.
 - Buprenorphine should be dosed sublingually and allowed to fully dissolve, not be swallowed. Up to 2 tablets can be administered sublingually at one time.
 - **Pregnancy Only:** Prescribe buprenorphine and NOT the buprenorphine/naloxone combination medication.
- Split Dosing:
 - Split dosing may be necessary for patient with acute or chronic severe pain
 - **Pregnancy Only:** As gestational age increases, plasma levels of buprenorphine change secondary to a decrease in half-life and an increase in clearance and volume of distribution. This generally occurs during the second and third trimester. As such, a provider may strongly consider splitting the daily buprenorphine dose to an AM and PM dose if the patient experiences withdrawal symptoms or cravings at night.

Breastfeeding Guidelines

Buprenorphine for opioid use disorder is not a contraindication for breastfeeding. Patients taking buprenorphine for opioid use disorder who are not currently abusing other substances and who wish to breastfeed should be encouraged to regardless of the buprenorphine dose. Current evidence shows that breastfeeding while on buprenorphine is beneficial to neonates with neonatal abstinence syndrome (NAS). Neonates receiving breast milk from these patients experience lower NAS scores, require less pharmacologic treatment such as morphine, and have shorter lengths of hospital stay.

Appendix A - Clinical Opioid Withdrawal Score (COWS)

PATIENT NAME:	DATE OF ASSESSMENT:
PATIENT DATE OF BIRTH:	MEDICAL RECORD NUMBER:

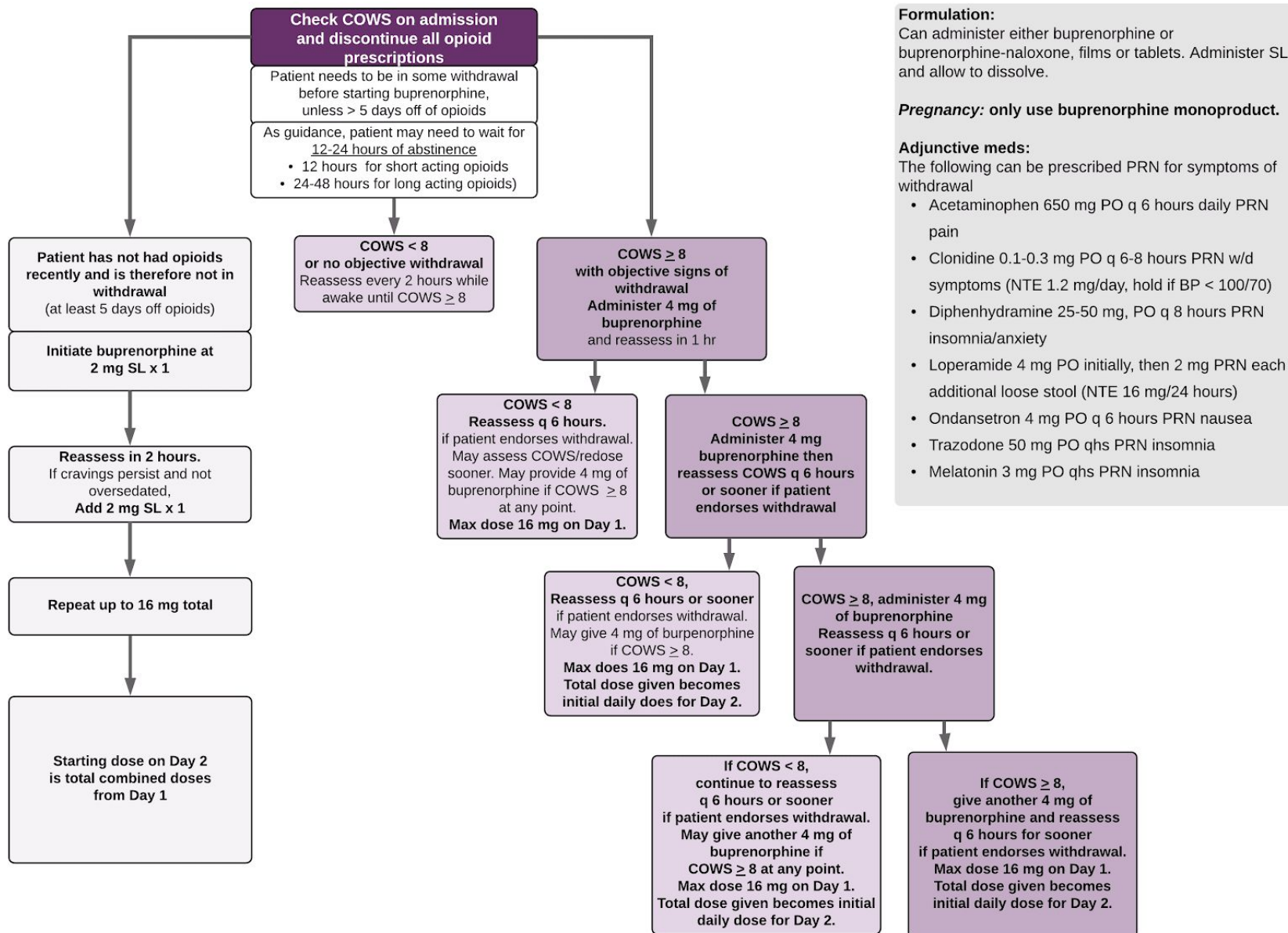
Clinical Opioid Withdrawal Score (COWS)

For each item, write in the number that best describes the patient's signs or symptom. Rate only the apparent relationship to opiate withdrawal. For example: *If heart rate is increased because the patient was jogging just prior to assessment, the increased pulse rate would not add to the score.*

Enter scores at time zero, 30 minutes after first dose, 2 hours after first dose, etc.	Time:	Time:	Time:	Time:
Resting Pulse Rate: Record beats per minute after patient is sitting or lying down for one minute • 0 - pulse rate 80 or below • 1 - pulse rate 81–100 • 2 - pulse rate 101–120 • 4 - pulse rate greater than 120				
Sweating: Over past ½ hour not accounted for by room temperature or activity • 0 - no chills or flushing • 1 - subjective chills or flushing • 2 - flushed or observable moistness on face • 3 - beads of sweat on brow or face • 4 - sweat streaming off face				
Restlessness: Observation during assessment • 0 - able to sit still • 1 - reports difficulty sitting still, but is able to do so • 3 - frequent shifting or extraneous movement of legs/arms • 5 - unable to sit still for more than a few seconds				
Pupil size • 0 - pupils pinned or normal size for light • 1 - pupils possibly larger than normal for light • 2 - pupils moderately dilated • 5 - pupils dilated that only rim of the iris is visible				
Bone or joint aches: If patient was having pain previously, only the additional component attributed to opiate withdrawal is scored • 0 - not present • 1 - mild/diffuse discomfort • 2 - patient reports severe diffuse aching of joints/muscles • 4 - patient is rubbing joints or muscles and is unable to sit still because of discomfort				
Runny nose or tearing: Not accounted for by cold symptoms or allergy • 0 - none present • 1 - nasal stuffiness or unusually moist eyes • 2 - nose running or tearing • 4 - nose constantly running or tears streaming down cheeks				
GI upset: Over last ½ hour • 0 - no GI symptoms • 1 - stomach cramps • 2 - nausea or loose stool • 3 - vomiting or diarrhea • 5 - multiple episodes of diarrhea or vomiting				
Tremor: Observation of outstretched hands • 0 - no tremor • 1 - tremor can be felt, but not observed • 2 - slight tremor observable • 4 - gross tremor or muscle twitching				
Yawning: Observation during assessment • 0 - no yawning • 1 - yawning once or twice during assessment • 2 - yawning three or more times during assessment • 4 - yawning several times/minute				
Anxiety or irritability • 0 - none • 1 - patient reports increasing irritability or anxiousness • 2 - patient obviously irritable or anxious • 4 - patient so irritable or anxious that participation in the assessment is difficult				
Gooseflesh skin • 0 - skin is smooth • 3 - piloerection of skin can be felt or hairs standing up on arms • 5 - prominent piloerection				
5—12 = mild; 13—24 = moderate; 25—36 = moderately severe; > 36 = severe withdrawal	TOTAL			
	OBSERVER INITIALS			

Quick Guide: Buprenorphine Starts in the Hospital

Appendix B



For clinical questions:

UCSF Substance Use Warm-line: 855-300-3595 or <https://tinyurl.com/yd4ymyx6> (M-F 9am-8pm ET)

Quick Guide: Buprenorphine Starts in the Hospital

Appendix B

Testing prior to first dose:

- ☐ Urine toxicology
- ☐ Liver function tests
- ☐ Urine pregnancy test
(PRN childbearing potential)
- ☐ HIV, Hep B, Hep C as indicated
- ☐ DSM 5 criteria for opioid use disorder
- ☐ CURES report
- ☐ **Pregnancy:** non-stress test or fetal heart tones as indicated

Contraindications/cautions:

Call experts as needed, may still start with support

- Allergy to buprenorphine
- Medically unstable, unable to tolerate mild withdrawal
- Methadone in last week
- AST or ALT > 5x upper limit normal
- Surgery in next 48 hours
- Acute severe pain
- Binge alcohol or benzo use

Patients started in the ED:

- If given total dose of <16 mg in ED, continue to follow day 1 algorithm
- If given total dose 16 mg in ED, hold additional doses on day 1, then day 2 start 16 mg qday
- If given total dose > 16 mg in ED, hold additional dosing until return of cravings/withdrawal, then start 16 mg qday
- If patient is experiencing pain may split dose TID

Day 2:

- Administer total daily dose from day 1 as single dose in am, or if patient is experiencing pain may split total daily dose TID
- Repeat COWS in 6 hours, if ≥ 8 administer additional 4 mg

Subsequent days:

- Administer total daily dose from previous day as single dose in am – split TID if ongoing pain
- Increase dose prn cravings/withdrawal/pain
- Decrease dose prn sedation, insomnia, adverse effects
- Typical max dose 24 mg

Discharge prescriptions:

Buprenorphine may only be prescribed on discharge by X licensed provider. Prescribe dose required in hospital as daily dose on discharge.

Example:

- Buprenorphine/naloxone 8 mg/2 mg film, 2 films SL qday, #14, 0 refills
- Naloxone 4 mg/0.1 ml intranasal PRN opioid overdose. Spray 0.1 ml into one nostril, call 911, if no response in 2-3 minutes repeat with second device in additional nostril. #1 pack of 2, 3 refills
- Consider pre-exposure HIV prophylaxis

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Inpatient Management of Opioid Use Disorder

Methadone and Buprenorphine Decision Guide (Non-pregnancy)



Appendix C – Non-Pregnancy Decision Guide

	Methadone	Buprenorphine
Retention in treatment	Higher in methadone ¹ , with possible contribution from increased structure of programs	May be slightly lower than methadone, retention improves at doses over 16mg
Office visits	Daily visits to maintenance treatment program, take-homes may be allowed if stable for long term (minimum 3 months). This can provide structure but some patients may dislike	Can range from daily to monthly depending on patient treatment needs, may be provided in primary care setting. Also available in some methadone clinics, increasing structure and decreasing diversion risk
Diversion potential	Low for directly observed therapy (DOT), high for take home	Low for DOT, moderate for take-homes, reduced by co-formulation with naloxone
Sedation/respiratory depression	At high doses in non-tolerant patients or slow metabolizers has potential for sedation, worse in combination with some medications	Ceiling effect for respiratory depression, therefore less risky (unless concurrent use of sedating drugs, e.g., alcohol/benzodiazepines)
Who can prescribe after discharge?	Opioid treatment program only	Any physician, NP, or PA who has been trained and possesses a DATA 2000 waiver (aka X-number)
Overdose risk from opioid replacement	Low-moderate ² , higher when initiating treatment or in combo with other medications ²	Low, increased by concurrent sedating medications
Mortality	Both options substantially decrease all-cause mortality over no treatment, methadone may have higher mortality but may be confounded ³	Both options substantially decrease all-cause mortality over no treatment, buprenorphine may have lower mortality but may be confounded
Risk of withdrawal when starting medication	None	Some, if not in withdrawal prior to starting may have precipitated withdrawal
Withdrawal potential when stopping medication	Moderate to severe	Low to moderate

Some patients may decline buprenorphine or methadone, but still be interested in medication assisted treatment. In these cases, one option is naltrexone. Oral naltrexone is more readily available and this has been shown to have very high drop-out rates so is not considered first line¹. IM may be effective in patients who have completed detox, but can be challenging to initiate and for patients to access. Naltrexone can only be started after a patient has completely withdrawn from opioids—roughly 5-7 day for short acting and 7-10 days for long acting. One option is to give naloxone as a trial before administering naltrexone, to make sure the patient doesn't experience precipitated withdrawal. Dosing usually begins with 25 mg on the first day, and is then increased to 50 mg daily. The most common side effects are nausea, vomiting, and headache. Retention in treatment is much worse than for buprenorphine or methadone.

¹ McLellan A, Arndt I, Metzger D, Woody G, O'Brien C. Treatment Retention among Patients Randomized to Buprenorphine/Naloxone Compared to Methadone in a Multi-Site Trial. *Addiction*. 2014; 109(1): 79–87.

² Sordo L, Barrio G, Bravo M, Indave B, Degenhardt L, Wiessig L, Ferri M, Pastor-Barriuso R. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. *BMJ*. 2017;357:j1550

³ Minozzi S, Amato Le Vecchi S, Davoli M, Kirchmayer, U, Verster A. Oral naltrexone maintenance treatment for opioid dependence. *Cochrane Database of Systematic Reviews*: Reviews. 2011.

Appendix D – Pregnancy Decision Guide

	Methadone	Buprenorphine
Efficacy	Opioid abstinence and a reduction in illicit opioid use, injection drug use, overdose deaths, and mortality	Opioid abstinence and a reduction in illicit opioid use, injection drug use, overdose deaths, and overall mortality
Retention in treatment	Higher in methadone (88% in the MOTHER study ¹), with possible contribution from structure of programs	Slightly lower than methadone (67% in the MOTHER study although dosing may have been subtherapeutic and most drop outs during titration) ¹
Office visits	Daily visits to OTP. Take-homes may be allowed if stable for long term (minimum 3 months) or a waiver is granted. Frequent visits provide structure, but some may dislike	Can range from daily to monthly depending on patient treatment needs, may be provided in primary care setting. Note, may be available at methadone clinics, increasing structure and decreasing diversion risk
Diversion potential	Low for directly observed therapy (DOT), high for take-homes	Low for DOT, moderate for take-homes
Maternal sedation/respiratory depression	At high doses in non-tolerant patients or slow metabolizers, there is potential for sedation, worse in combination with some medications	Less sedating. Ceiling effect for respiratory depression, therefore less risky (unless concurrent use of sedating drugs, e.g., alcohol/benzodiazepines/CNS depressants)
Who can prescribe after discharge?	Opioid treatment program only	Any physician, NP, or PA who has been trained and possesses a DATA 2000 waiver (aka an X-number)
Overdose risk from opioid replacement	Low-moderate, higher when initiating treatment or in combo with other medications	Low, increased by concurrent sedating medications
Mortality	Both options substantially decrease all-cause mortality over no treatment, methadone may have higher mortality in the general population, but may be confounded ²	Both options substantially decrease all-cause mortality over no treatment, buprenorphine may have lower mortality in the general population, but may be confounded
Withdrawal if detoxing	Moderate to severe	Low to moderate
Risk of withdrawal when starting	None	Mild to moderate withdrawal required. If not in withdrawal prior to starting, may have precipitated withdrawal
Neonatal Outcomes ²	<p>Reduced preterm birth and low birth weight rates</p> <p>Higher doses do NOT correlate with more NAS</p> <p>NAS is 75% - in MOTHER study:</p> <ul style="list-style-type: none"> - 17.5 day average length of hospitalization - 10.4 mg morphine required during hospitalization¹ 	<p>Reduced preterm birth and low birth weight rates</p> <p>Later average gestational age and higher average birth weight than methadone</p> <p>Higher doses do NOT correlate with more NAS</p> <p>NAS less severe than for methadone – in MOTHER study:</p> <ul style="list-style-type: none"> - 10 day average length of hospitalization - 1.1 mg morphine required during hospitalization¹

Note: Naltrexone is not a recommended treatment option in pregnancy.

¹ Jones HE, Kaltenbach K, Heil SH, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. N Engl J Med. 2010;363(24):2320-31.

² Sordo L, Barrio G, Bravo M, Indave B, Degenhardt L, Wiessig L, Ferri M, Pastor-Barriuso R. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. BMJ. 2017;357:j1550