MEDICATIONS IN OPIOID USE DISORDER

Treating Patients with Methadone, Naltrexone or Buprenorphine

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Disclosure Statement

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Objectives

1. Describe the role and pharmacological characteristics of medications used to treat opioid use disorder (OUD)

2. Compare FDA approved medications for OUD

3. Develop a treatment plan for a patient with OUD given a patient case scenario

Common Abbreviations

ASAM	American Society of Addiction Medicine
AUD	Alcohol use disorder
CARA	Comprehensive Addiction and Recovery Act
CNS	Central nervous system
DATA 2000	Drug Addiction Treatment Act of 2000
DEA	Drug Enforcement Agency
HHS	(U.S. Department of) Human Health Services
MAT	Medication assisted treatment
MSW	Medically supervised withdrawal
NAS	Neonatal abstinence syndrome
OBOTs	Office-based opioid treatment programs
ORAEs	Opioid-related adverse events
OS	Opioid Stewardship
OUD	Opioid Use Disorder
SAMHSA	Substance Abuse and Mental Health Services Administration
TIP	Treatment Improvement Protocol (SAMHSA)
XR-NTX	Extended-release naltrexone injection

Source: https://www.asam.org/quality-care/clinical-guidelines/national-practice-guideline

Common Terms & Definitions

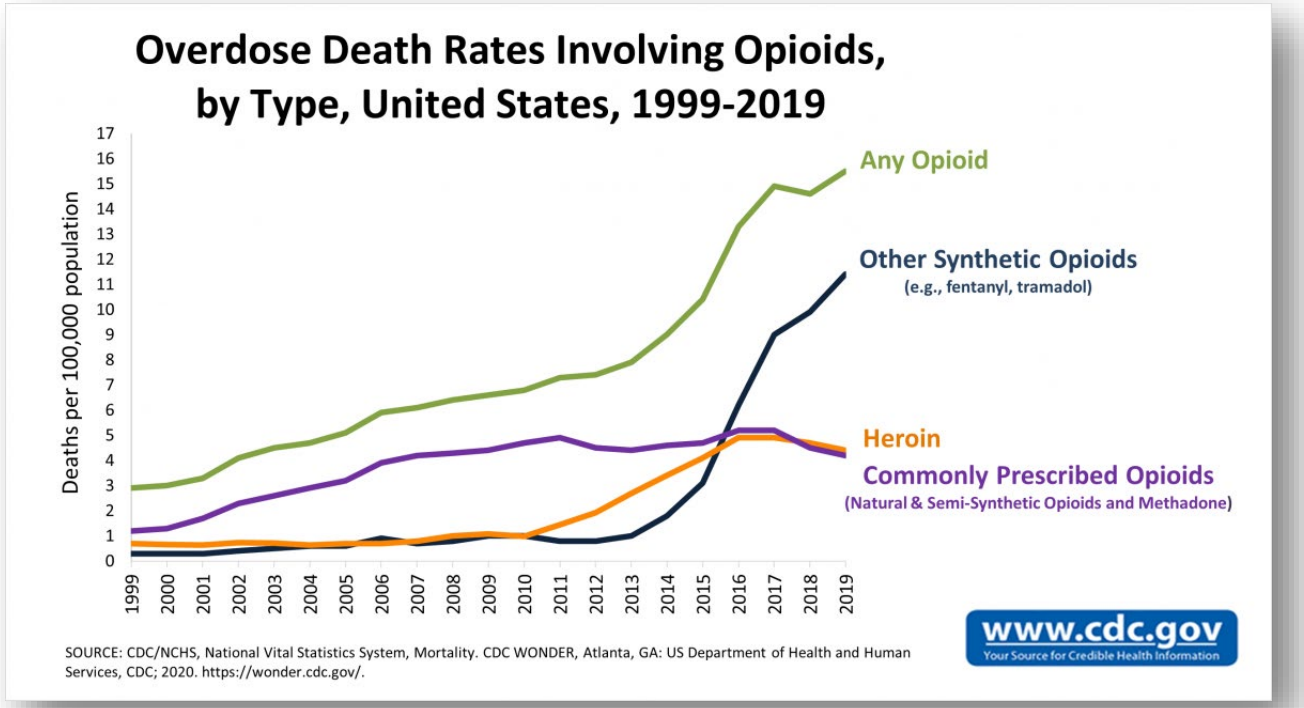
Abuse liability	The likelihood that a medication with CNS activity will cause desirable psychological effects (such as euphoria or mood changes) that promote the medication's misuse
Addiction	A primary, chronic disease of brain reward, motivation, memory, and related circuitry; often involves cycles of relapse and remission
Bioavailability	Proportion of medication administered that reaches the blood stream
Cross tolerance	Potential for people tolerant to one opioid (e.g., heroin) to be tolerant to another (e.g., methadone)
Induction	Process of initial dosing with medication for OUD Treatment until the patient reaches a state of stability; also called initiation
Intrinsic activity	The degree of receptor activation attributable to drug binding (e.g., full agonist, partial agonist, antagonist)
Maintenance treatment	Providing medications to achieve and sustain clinical remission of signs/symptoms of OUD and support the individual process of recovery without a specific endpoint
Medically supervised withdrawal	Formerly known as "detoxification"; Using an opioid agonist (or alpha-2 adrenergic agonist) in tapering doses or other medications to help a patient discontinue illicit or prescription opioids
Office-based opioid treatment	Providing medication for OUD in outpatient settings other than certified OTPs
Opioid blockade	Blunting or blocking of the euphoric effects of an opioid through opioid receptor occupancy by an opioid agonist or antagonist
Opioid receptor agonist	A substance that has affinity for and stimulates physiological activity at receptors in the central nervous system that are normally stimulated by opioids
Opioid receptor antagonist	A substance that has an affinity for opioid receptors in the central nervous system without producing the physiological effects of opioid agonists
Opioid Treatment Program (OTP)	An accredited treatment program with SAMHSA certification and DEA registration to administer and dispense opioid agonist medications that are approved by the FDA to treat opioid addiction (e.g., buprenorphine, methadone)
Opioids	All natural, synthetic, and semisynthetic substances that have effects similar to morphine. They can be used as medications having such effects (e.g., methadone, buprenorphine, oxycodone)
Receptor affinity	Strength of the bond between a medication and its receptor; affects receptor occupancy and displacement

Source: https://www.asam.org/quality-care/clinical-guidelines/national-practice-guideline

Background – OUD Statistics

In 2019, an estimated **1.6 million people** aged 12 or older had OUD in the United States.

- The number of drug-related overdose deaths rose to an all-time high of **100,306 deaths** from April 2020 to April 2021
- The development of OUD, the spread of HIV and hepatitis infections, and increasing number of overdose deaths constitute a public health crisis



Sources: https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2021/20211117.htm | https://www.cdc.gov/opioids/data/index.html

Background – DSM5 Criteria for OUD

- ❑ Opioids are often taken in **larger amounts or over a longer period of time** than intended
- ❑ There is a persistent desire or **unsuccessful efforts to cut down** or control opioid use
- ❑ A great deal of time is spent in **activities necessary to obtain the opioid**, use the opioid, or recover from its effects
- ❑ **Craving**, or a strong desire to use opioids
- ❑ Recurrent opioid use resulting in **failure to fulfill major role obligations at work, school, or home**
- ❑ Continued opioid use despite having persistent or **recurrent social or interpersonal problems** caused or exacerbated by the effects of opioids
- ❑ Important **social**, **occupational**, or **recreational** activities are given up or reduced because of opioid use
- ❑ Recurrent opioid use in situations in which it is **physically hazardous**
- ❑ **Continued use** despite knowledge of having persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by opioids
- ❑ **Tolerance** as defined by a) a need to markedly increase amounts of opioids to achieve intoxication or a desired effect or b) markedly diminished effect with continued use of the same amount of an opioid
- ❑ **Withdrawal**, as manifested by either a) the characteristic opioid withdrawal syndrome or b) the same (or a closely related) substance are taken to relieve or avoid withdrawal symptoms

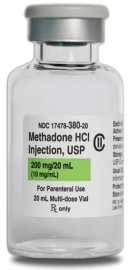
____ **Total Boxes Checked:** **Mild**: 2-3 symptoms **Moderate**: 4-5 symptoms **Severe**: 6+ symptoms

Sources: https://www.ncbi.nlm.nih.gov/books/NBK519702/ | https://www.asam.org/docs/default-source/education-docs/dsm-5-dx-oud-8-28-2017.pdf
https://www.ncbi.nlm.nih.gov/books/NBK535277/box/p2.b4/?report=objectonly

Role of OUD Treatment

OUD medications have been shown to reduce illicit opioid use, retain people in treatment, and reduce risk of opioid overdose death better than treatment with placebo or no medication. The goal with treatment is remission leading to lasting recovery.

- There is no one size fits all approach to OUD treatment
- OUD medication can be taken on a short-term or long-term basis
- OUD medications have been shown to be cost effective
- Patients taking medication for OUD are considered to be in recovery
- Several barriers contribute to the underuse of medication for OUD



Sources: https://store.samhsa.gov/sites/default/files/SAMHSA_Digital_Download/PEP21-02-01-002.pdf | https://www.acepnow.com/article/suboxone-101-the-skinny-on-this-opioid-dependence-drug/
https://www.henryschein.com/us-en/medical/p/pharmacy/rx/vivitrol-inj-suspension-q-25/1366569 | https://www.henryschein.com/Products/1358787_01_FRONT_600x600.jpg

OUD Medication Introduction

Methadone

Full Agonist at Mu-Opioid Receptor

Typically for patients with OUD who are physiologically dependent on opioids and who meet **federal criteria for OTP admission**.

- High retention in treatment, suppresses illicit opioid use and reduces overdose mortality
- Patient's doses will start low and build up slowly to avoid oversedation
- Treatment is initiated over several weeks
- Only SAMHSA - certified OTPs can provide methadone for daily onsite administration or at home self-administration for stable patients

Naltrexone

Full Antagonist at Mu-Opioid Receptor

Typically for patients with OUD who have **abstained** from short-acting opioids for at least 7-10 days and long-acting opioids for at least 10-14 days.

- XR-NTX has retention in treatment and suppresses illicit opioid use, no evidence to reduce mortality
- Most concerns with initiation requirements, can precipitate withdrawal
- Causes no opioid effects
- Given once every 4 weeks
- Oral naltrexone not as effective as XR-NTX
- No prescribing waiver requirement

Buprenorphine

Partial Agonist at Mu-Opioid Receptor

Typically for patients who are physiologically dependent on opioids.

- High retention in treatment, suppresses illicit opioid use and reduces overdose mortality
- Need to be in opioid withdrawal to receive their first dose to avoid precipitated opioid withdrawal
- Has ceiling effect limiting opioid effects
- Relatively fast induction period
- Requires DEA X-waiver to prescribe for OUD (and REMS program registration for long-acting formulations)
- Good medication candidate to initiate in the ED

TM = Transmucosal

Sources: https://store.samhsa.gov/sites/default/files/SAMHSA_Digital_Download/PEP21-02-01-003.pdf

Patient Selection

No evidence clearly predicts which patients will respond best to a specific OUD treatment vs. other pharmacotherapies.

- Medications should be reserved for those with moderate-to-severe OUD with physical dependence
- Patients who responded well to a specific agent in the past should be considered for that treatment
- Unsuccessful treatment experiences with a specific agent in the past do not necessarily indicate that that agent will be ineffective again
- Pregnant women should be considered for methadone or buprenorphine treatment
- Methadone or buprenorphine treatment through OTPs may be best for patients who need a higher level of outpatient support or supervision of medication adherence

Informed Consent

Treatment Agreement Forms

- Inform patients of OUD diagnosis and disorder
- Disclose risk and benefits of the selected OUD treatment, alternative OUD meds, and non-pharmacological treatments
- Understand that discontinuing increases risk of OD and death
- Store medication securely
- Alert providers if they discontinue

For **methadone**: Daily requirements, safe storage of take-home doses

For **buprenorphine** and **naltrexone**: Patients need to understand that they must be in opioid withdrawal to avoid precipitated withdrawal

Sources: https://nida.nih.gov/sites/default/files/SamplePatientAgreementForms.pdf
https://store.samhsa.gov/sites/default/files/SAMHSA_Digital_Download/PEP21-02-01-002.pdf

Duration of OUD Treatment

Patients can take OUD medications on a short-term or long-term basis, but the optimal length is not known.

- Longer lengths of treatment are associated with superior treatment outcomes as patients who discontinue OUD medication generally return to illicit opioid use
- Patients should continue their OUD medication if they want to be on treatment, continue to benefit from treatment, and develop no contraindications
- Once stabilized on OUD medication, many patients stop using illicit opioids completely

Given the often-chronic nature of OUD and the potentially fatal consequences of unintended opioid overdose, it is critical that a patient's length of time in treatment is based on their individual needs.

Sources: https://www.healthquality.va.gov/guidelines/MH/sud/VADoDSUDCPGRevised22216.pdf
https://nida.nih.gov/sites/default/files/podat_1.pdf

Medically Supervised Withdrawal (MSW)

Formerly known as detoxification, this process gradually decreases the dose until the medication is discontinued over days or weeks on an outpatient or inpatient basis. It is appropriate when patients:

- Prefer it to treatment without medications, after they have been told the risks and benefits of this approach compared with treatment with medications
- Wish to start XR-NTX, which is also FDA approved for alcohol use disorder (AUD)
- Are entering a controlled environment or workplace that disallows opioid agonists

Medications that can be used for MSW include:

- **Methadone** at an individualized dose between 20 - 30 mg/day and gradually reduced over 6 - 10 days
- **Buprenorphine** at an adequate dose (start at 2 - 4 mg/day and titrate to 4 - 16 mg/day) to lessen withdrawal symptoms and then reduced over several days or more (variable tapering schedule)
- **Clonidine** 0.1 - 0.3 mg every 6 - 8 hours to treat symptoms in place of opioid agonists

Short-term MSW alone is not recommended because of its high rates of return to illicit opioid use.

Disclaimer: Clonidine used “off-label” for opioid withdrawal

Sources: https://www.healthquality.va.gov/guidelines/MH/sud/VADoDSUDCPGRevised22216.pdf | https://pubmed.ncbi.nlm.nih.gov/19588330/
https://www.asam.org/quality-care/clinical-guidelines/national-practice-guideline | https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022410s033,020732s019,020733s023lbl.pdf

Signs & Symptoms of Opioid Withdrawal

The **Clinical Opiate Withdrawal Scale (COWS)** and **Clinical Institute Narcotic Assessment (CINA)** Scale Scores can be used to screen for opioid withdrawal status.

Signs

- Runny nose
- Tearing
- Yawning
- Sweating
- Tremor
- Vomiting
- Piloerection
- Pupillary dilation (mydriasis)

Symptoms

- Skin crawling
- Abdominal cramps
- Temperature changes
- Nausea
- Vomiting
- Diarrhea
- Bone/muscle pain
- Dysphoria
- Craving for opioids

Sign or Symptom	COWS	CINA
Anxiety or irritability	Yes	No
Temperature changes	No	Yes
GI upset	Yes	Yes
Restlessness	Yes	Yes
Bone or joint aches	Yes	Yes
Sweating	Yes	Yes
Runny nose/ tearing	Yes	Yes
Tremor	Yes	Yes
Gooseflesh	Yes	Yes
Yawning	Yes	Yes
Pupil size	Yes	No
Pulse rate	Yes	Yes
Systolic blood pressure	No	Yes
Maximum possible score	48	30 + Pulse/10 + SBP/10

COWS Score: 5 to 12 = mild; 13 to 24 = moderate; 25 to 36 = moderately severe; more than 36 = severe withdrawal. **CINA Score**: minimum = 0, maximum = 31

Sources: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2774236/ | https://pubmed.ncbi.nlm.nih.gov/3687892/

Medications that Assist with Withdrawal

During medically supervised withdrawal, ancillary medications can treat some of the withdrawal symptoms.

Opioid Agonist Alternative	Clonidine
Nausea	Ondansetron, metoclopramide *(avoid promethazine)*
Diarrhea	Bismuth, loperamide
Abdominal Cramping	Dicyclomine
Anxiety, Irritability, Sweating	Clonidine
Insomnia	Trazodone, diphenhydramine
Pain	NSAIDs (Ibuprofen)
Muscle Spasms	Cyclobenzaprine

A calm, quiet environment can help patients overcome most symptoms of acute opioid withdrawal and decrease the need for pharmacological interventions.

Disclaimer: Clonidine used “off-label” for opioid withdrawal, trazodone used “off-label” for sleep

Sources: https://www.uptodate.com/contents/medically-supervised-opioid-withdrawal-during-treatment-for-addiction

General Prescribing Information

Methadone	Naltrexone	Buprenorphine
Schedule II Drug • Only available at federally certified OTPs for outpatient use • Can be used in the acute inpatient hospital setting for OUD treatment	**Prescription Drug** • Any prescriber can offer naltrexone • Not included in OTP regulations • Can be used in office-based treatment or OTPs	**Schedule III Drug** • OTPs can administer and dispense buprenorphine without a federal waiver • Requires federal X waiver to prescribe outside of OTPs; used in ED and OBOTs • Long-acting formulations require separate REMS program; dispenses through restricted distribution programs

Only physicians; nurse practitioners; physician assistants; and, until **October 1, 2023**, clinical nurse specialists, certified registered nurse anesthetists, and certified nurse midwives can prescribe buprenorphine for OUD. They must get a federal waiver to do so.

- As of 2021, practitioners can obtain a data waiver for up to 30 patients without the typical required training, but it limits them to only 30 patients
- **DATA 2000, CARA, and 21 CFR 1306.07** are important policies in regulations behind dispensing and administering narcotics for OUD

OBOTs = Office-Based Opioid Treatment

Sources: https://www.govinfo.gov/app/details/CFR-1998-title21-vol9/CFR-1998-title21-vol9-sec1306-07 | https://www.law.cornell.edu/cfr/text/21/1306.07
https://store.samhsa.gov/sites/default/files/d7/priv/pep15-fedguideotp.pdf | https://www.asam.org/quality-care/clinical-guidelines/national-practice-guideline

OUD Medication Summary Table

Generic/ Trade Name	Formulations	FDA Indications	Dosing
Methadone (Methadose, Dolophine)	Liquid concentrate, tablet, oral solution of powder, dispersible tablet	Medically supervised withdrawal and maintenance treatment of opioid dependence	Once daily (can split dose to twice daily)
Generic **buprenorphine monoproduct**	Sublingual tablet	Treatment of opioid dependence	Once daily
Generic **buprenorphine/naloxone**	Sublingual tablet, film	Treatment of opioid dependence	Once daily
Buprenorphine/naloxone (Zubsolv)	Sublingual tablet	Treatment of opioid dependence	Once daily
~~**Buprenorphine/naloxone** (Bunavail)~~	~~Buccal film~~	~~Treatment of opioid dependence~~	~~Once daily~~
Buprenorphine/naloxone (Suboxone)	Sublingual film (can also be administered buccally)	Treatment of opioid dependence	Once daily
Buprenorphine (Probuphine)	Implant	Maintenance treatment of opioid dependence in clinically stable patients taking 8 mg/day or less of Suboxone equivalents	Implants last for 6 months, a second set can be inserted
Extended-release injection **buprenorphine** (Sublocade)	Subcutaneous injection in abdominal region	Treatment of moderate-to-severe OUD among patients taking TM buprenorphine for at least 7 days	Monthly
Oral **naltrexone**	Oral tablet	Blocks the effects of administered opioid agonists	Once daily
XR-NTX (Vivitrol)	Intramuscular injection	Prevent return to opioid dependence after medically supervised opioid withdrawal	Once monthly

Source: https://store.samhsa.gov/sites/default/files/SAMHSA_Digital_Download/PEP21-02-01-003.pdf

Assessment Question #1

How is Naltrexone Administered?

A. Intravenous injection

B. Intramuscular injection

C. Subdermal implant

D. Buccal tablet

Assessment Question #1

How is Naltrexone Administered?

A. Intravenous injection

B. Intramuscular injection

C. Subdermal implant

D. Buccal tablet

METHADONE

Methadone Overview

Methadone has the largest and oldest evidence base of all treatment approaches to opioid addiction. Higher doses are associated with superior outcomes.

- Research shows that methadone treatment is associated with reduced mortality, criminal behavior, and HIV seroconversion
- Compared to buprenorphine, methadone **retains patients in treatment significantly longer** and **equally reduces illicit opioid use**. Methadone also retains patients and reduces illicit opioid use more effectively than placebo, medical supervised withdrawal, or no treatment
- In the United States, only OTPs (~1500 in the US) can offer methadone to treat OUD, but all providers who may care for patients with OUD should be familiar with this treatment
- Originally, methadone prescribed from OTPs were not reported to the PDMP but now it is possible to if the state requires it

MOA	Long-acting mu-opioid receptor full agonist that reduces opioid craving and withdrawal and blunts/blocks the effects of illicit opioids; does not have a ceiling effect
Drug Classification	Schedule II Controlled Medication
Available Formulations	**Concentrate** (10 mg/mL), **injection solution** (10 mg/mL), **oral solution** (5 mg/5 mL, 10 mg/5 mL), **oral tablet** (5 mg, 10 mg), **soluble tablet** (40 mg)

Sources: https://pubmed.ncbi.nlm.nih.gov/22065255/ | https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3271614/ | https://online.lexi.com

Methadone Pharmacology

Pharmacokinetics	• Wide individual variability: Half-life can range from 8-59 hours; average is 24 hours • **Methadone has no ceiling effect - Increasing doses produce maximal physiological effects at the opioid receptors** • Before the achievement of steady state (5 days), release from tissue reservoirs can lead to increasing serum plasma levels/toxicity, even if the daily dose has not changed
Dosing Considerations	**OTP Criteria** (can waive for certain people); patients younger than 18 Initial dose: 2.5 mg to 30 mg/day; Maintenance dose: 60 mg to 120 mg/day
Contraindications	Allergy, acute or severe bronchial asthma, GI obstruction, significant respiratory depression

Precautions and Warnings	• Methadone is a respiratory depressant (RD)
	• Patients who are older, cachectic, or have COPD are more susceptible to RD and should be treated with lower doses
	• Use lower-than-usual starting dose in individuals with no or low opioid tolerance (5 to 10 mg)
	• **Increase doses slowly and with careful monitoring for patients who:**
	  • Have not used opioids for 5 or more days (leaving a controlled environment)
	  • Do not use opioids daily
	  • Use weaker opioids (codeine)
	• Do not determine doses by analgesic equivalence dose conversion tables for patients using high doses of RX opioids, whether by prescription or illicitly
	• **Other warnings: QTc Prolongation**, **concurrent BZD/alcohol**, accidental ingestion, neonatal abstinence syndrome (NAS), misuse and diversion risk, physical dependence, sedation, adrenal insufficiency

Sources: https://online.lexi.com | https://www.asam.org/quality-care/clinical-guidelines/national-practice-guideline

Methadone Pharmacology

Drug interactions	Most clinically significant interactions (many with **inhibitors**/**inducers** of CYP3A4): • **Antiretrovirals**: abacavir, efavirenz, lopinavir, nevirapine, didanosine, zidovudine, etc. (most are inducers) • **Antidepressants**: TCAs, SSRIs (inhibitors), SNRIs, MAOIs, • **Antibiotics**: azithromycin, ciprofloxacin, clarithromycin, erythromycin, rifampin (all inhibitors besides rifampin, an inducer) • **Antifungals**: fluconazole, ketoconazole (all inhibitors) • **Anticonvulsants**: carbamazepine, phenobarbital, phenytoin (all inducers) • **Antiarrhythmics**: amiodarone (inhibitor), procainamide, quinidine • **Benzodiazepines** • **Barbiturates** • **Cimetidine** (inhibitor) • **Naltrexone** Medications that can induce QTc prolongation: haloperidol, ondansetron, etc.
Side Effects	Constipation, hyperhidrosis, nausea, sweating, sexual dysfunction or decreased libido, drowsiness, amenorrhea, weight gain, edema, respiratory depression, **QT prolongation**, severe hypotension, misuse potential, neonatal abstinence syndrome (NAS)

Sources: https://online.lexi.com | https://www.asam.org/quality-care/clinical-guidelines/national-practice-guideline

Initiating & Maintaining Methadone Treatment

First Day of Induction

The first dose of methadone should reduce opioid withdrawal symptoms (induction should be performed cautiously, it is impossible to judge a patient's level of tolerance with certainty). Induction should not be based on a standing order.

With opioid tolerance:

- Generally, give between **10 - 30 mg** (30 mg is the maximum first dose). After the first dose, observe for 2-4 hours to see if the dose is sedating or relieves withdrawal signs. Can give an additional 5 - 10 mg depending on the patient's response. Total first daily dose rarely exceeds 30 mg
- Lower range of **10 - 20 mg** may be appropriate in patients who are 60 and older, have lower levels of opioid tolerance based on recent history, use sedating medications, have alcohol use disorder, or have medical conditions that cause hypoxia, hypercapnia, or cardiac arrhythmias

Without opioid tolerance:

- Consider XR-NTX or buprenorphine instead of methadone
- If XR-NTX and buprenorphine are unavailable or the patient prefers methadone, consider **starting at 2.5 - 10 mg (typically) 5 mg daily dose**
- This dose should be titrated much more slowly than for patients who are opioid tolerant (**increase 5 mg every week based on patient response**)

Sources: https://online.lexi.com | https://store.samhsa.gov/sites/default/files/SAMHSA_Digital_Download/PEP21-02-01-002.pdf
https://www.asam.org/quality-care/clinical-guidelines/national-practice-guideline

Initiating & Maintaining Methadone Treatment

Dose Titration (Weeks 1 - 2)

- **Goal is to avoid sedation at peak serum levels, gradually extend time without opioid withdrawal symptoms and craving**
- The American Society of Addiction Medicine expert panel recommends **increasing the methadone dose by ≤ 5 mg every 5 or more days**
- Patients who report relief from withdrawal 4 to 12 hours after their last dose may benefit from staying at that same dose for a few days

Dose Titration (Weeks 3 - 4)

- **Increase dose further in 5 mg increments about every 3 to 5 days based on the patient's symptoms** of opioid withdrawal or sedation
- Patients who miss > 4 doses must be reassessed and may need to restart the dose induction process from **Day 1**
- **Measuring serum methadone levels:** Draw peak and trough blood specimens at 3 hours and 24 hours after dose administration. Peak: trough ratios above 2:1 may indicate rapid metabolism
- Consider measuring serum methadone levels in patients stable on a methadone dose who still report feeling drowsy 2 to 4 hours after dose administration but develop craving or withdrawal symptoms before the next dose is due. Consider splitting the total dose for twice daily dosing

Sources: https://online.lexi.com | https://store.samhsa.gov/sites/default/files/SAMHSA_Digital_Download/PEP21-02-01-002.pdf
https://www.asam.org/quality-care/clinical-guidelines/national-practice-guideline

Initiating & Maintaining Methadone Treatment

Dose Stabilization (Week 5+)

- Once the patient achieves an adequate dose, extended continuation is possible without dose adjustment
- Continuing goals: avoid sedation, eliminate withdrawal/craving, blunt/block euphoric effects of illicit opioids
- As illicit opioid use stops and stabilization is achieved, the patient may wish to lower the dose to reduce any unpleasant side effects
- Typical stabilization doses of at least 60 mg are associated with greater treatment retention
    - **80 - 120 mg is the typical daily range**, some patients benefit from higher daily doses

Take Home Medications

- OTPs can provide gradually increasing numbers of take-home doses to patients, provides powerful incentive for patients to achieve treatment goals
- Furthers patient's recovery goals by allowing them a balance in life activities
- Some states have additional regulations on top of the federal OTP regulations/conditions for take home doses
- Benefits must outweigh the risks

Sources: https://online.lexi.com | https://store.samhsa.gov/sites/default/files/SAMHSA_Digital_Download/PEP21-02-01-002.pdf
https://www.asam.org/quality-care/clinical-guidelines/national-practice-guideline

Discontinuing / Tapering Methadone

Individualize pace of methadone dose reduction to patient's responses

- **Decrease methadone gradually by 5 - 10% every 1 - 2 weeks.** Once patients reach a relatively low dose (often between 20 - 40 mg), they may begin to feel more cravings
- Some patients may choose to switch to buprenorphine or naltrexone (see below)

Other considerations with discontinuing/ tapering:

- Logistics, costs, side effects
- Opinions of family/friends
- Desire to switch to buprenorphine or XR-NTX treatment
- Caution patients who are not yet stable against discontinuing treatment due to risk of returning to illicit opioid use and increased chance of OD
- Create plan to collaborate with stable patients who wish to D/C treatment
- Provide increasing psychosocial and recovery supports

- Gradually taper dose
  - **To switch to buprenorphine**, gradually taper to 30 - 40 mg and remain on that dose for 7+ days. The patient should be in mild withdrawal prior to starting buprenorphine (24 - 48 hours after last dose of methadone). Initiate buprenorphine at 2 mg
  - **To switch to naltrexone**, taper/discontinue methadone and wait 7 - 14 days before initiating treatment with naltrexone
- Discontinue dose reduction if necessary
- Returning to med treatment after discontinuation if they return to illicit opioid use
- Increasing dosage if destabilization occurs

Sources: https://online.lexi.com | https://www.asam.org/quality-care/clinical-guidelines/national-practice-guideline

Assessment Question #2

The lower range of initial methadone doses (10 mg to 20 mg) is best for patients who:

A. Are younger than 60 years of age

B. Have higher levels of opioid tolerance based on their recent history

C. Do not use sedating medications

D. Have alcohol use disorder

Assessment Question #2

The lower range of initial methadone doses (10 mg to 20 mg) is best for patients who:

A. Are younger than 60 years of age

B. Have higher levels of opioid tolerance based on their recent history

C. Do not use sedating medications

D. Have alcohol use disorder

METHADONE SUMMARY

- Methadone is the oldest OUD medication and considered a gold standard for treatment
- Methadone is a mu-opioid receptor full agonist with a very long half-life (24 - 36 hours)
- Methadone is shown to lower overdose mortality and suppress illicit opioid use and has a high retention rate
- Dosing should start low and go slow - increase doses gradually over several weeks (**initial dose is 2.5 - 30 mg/day**)
- **Eventual target dose is typically between 60 - 120 mg/day** but the effective dose range is broad but balances withdrawal symptoms with sedation
- In general, higher doses of methadone are more effective than lower doses after induction is complete and patients will develop tolerance and physical dependence with maintenance use
- Methadone use has concerns with QTc prolongation and respiratory depression (no ceiling effect); has more drug interactions than buprenorphine or naltrexone
- Methadone can be considered for pregnant patients with OUD
- Only SAMHSA-certified OTPs can provide methadone to patients on a daily basis; patients can “earn” take-home doses

NALTREXONE

Naltrexone Overview

XR-NTX (injectable naltrexone formulation) is approved for preventing return to opioid dependence after medically supervised withdrawal; however, is not shown to reduce overdose or serious opioid-related acute care at 3 or 12 months of use.

- Oral naltrexone is not used widely because of low rates of patient acceptance, difficulty in achieving abstinence for the necessary time before treatment initiation, and high rates of nonadherence
- May be advantageous to initiate in controlled environments compared to starting in the outpatient community setting
- Naltrexone is also approved for alcohol use disorder and may be useful to patients with both

MOA	• Competitive mu-opioid receptor antagonist with strong receptor affinity; exerts no opioid effects • Will not alleviate withdrawal symptoms, will not cause withdrawal when stopped, cannot be diverted • Naltrexone can block effects of opioid agonists; but due to the competitive activity at the receptor, **the blockade can potentially be overridden with high doses of opioids**
Drug Classification	Prescription drug (not a controlled substance)
Available Formulations/ Strengths	**Oral tablet** (25 mg, 50 mg), **Intramuscular suspension** (380 mg)
Dosing	• Appropriate patients should have an adequate period of abstinence with no signs of opioid withdrawal prior to administration • **Oral**: 25 or 50 mg once daily, **IM Injection**: 380 mg once monthly or every 4 weeks • Repeated administration causes no accumulation of naltrexone or its metabolites

Sources: https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2760032 | https://online.lexi.com
https://store.samhsa.gov/sites/default/files/SAMHSA_Digital_Download/PEP21-02-01-002.pdf

Naltrexone Pharmacology

Contraindications	• Hypersensitivity to XR-NTX suspension and diluent • Current pain treatment with opioid analgesics • Current physiological opioid dependence or acute opioid withdrawal • Severe hepatic impairment • Naloxone challenge or oral naltrexone dose causing opioid withdrawal symptoms • Patients who test positive for current opioid use are not contraindicated for the induction as long as they pass the naloxone challenge, indicating that they are not opioid dependent
Precautions/ Warnings	• Patients who are pregnant (avoid use) • Patients are vulnerable to OD death after completing the every 4-weeks or once monthly dosing period, missing a dose, or stopping treatment • Overdose can occur with overriding the blockade • Injection site reactions, hypersensitivity reactions • Precipitated opioid withdrawal • Hepatitis has been associated with XR-NTX; caution in patients with moderate-to-severe renal impairment • Monitor for depression and suicidal ideation; dysphoria (oral naltrexone) • Emergency pain treatment; regional anesthesia or nonopioid analgesics are alternatives to opioid analgesics
Side effects	Nausea, anxiety, insomnia, precipitated opioid withdrawal, hepatotoxicity, vulnerability to opioid overdose, depression, suicidality, muscle cramps, dizziness/syncope, somnolence/sedation, anorexia, appetite disorders; **IM**: pain, swelling, induration

Sources: https://online.lexi.com | https://store.samhsa.gov/sites/default/files/SAMHSA_Digital_Download/PEP21-02-01-002.pdf

Naloxone Challenge

The naloxone challenge can be used to assess a lack of physical opioid dependence. Naloxone can be given IV, IM, SC to patients who report an adequate period of opioid abstinence and have a negative opioid urine test. It is not recommended for pregnant OUD patients.

Intravenous Administration of Naloxone:

1. Draw 0.8 mg, **inject 0.2 mg intravenously**. If withdrawal signs/symptoms are present, stop and treat symptomatically
    1. If no withdrawal signs/symptoms, inject the remaining 0.6 mg and observe for 20 minutes
2. **If withdrawal present:**
    1. Stop and treat symptomatically; can **repeat in 24 hours** or the patient can be considered for an opioid agonist treatment
3. **If no withdrawal:**
    1. Oral naltrexone: Give the patients 2 x 25 mg tablets (take one tablet on each of the next 2 days) and enough 50 mg tablets (take one 50 mg tablet daily starting on the third day) until they can fill their prescription for oral naltrexone
    2. XR-NTX: Administer 380 mg into the upper outer quadrant of the buttock
4. Instruct the patient about the risk of OD and death if they use opioids to override the blockade

Subcutaneous Administration of Naloxone:

1. Inject **0.8 mg subcutaneously** and wait 20 minutes
2. **If withdrawal present:** Stop and **repeat in 24 hours** or consider opioid agonist treatment
3. **If no withdrawal:** Give the oral naltrexone or XR-NTX (see above dosing instructions)

Sources: https://www.healthquality.va.gov/guidelines/MH/sud/VADoDSUDCPGRevised22216.pdf | https://pubmed.ncbi.nlm.nih.gov/19588330/
https://www.asam.org/quality-care/clinical-guidelines/national-practice-guideline | https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022410s033,020732s019,020733s023lbl.pdf

Initiating & Maintaining Naltrexone Treatment

Initiating XR-NTX treatment

- Before preparing and administering XR-NTX, keep at room temperature for 45 minutes, use correct needle length, use proper aseptic technique, use proper gluteal IM injection technique, and never inject IV or SC. Repeat injection every 4 weeks or once per month
- Use a 1.5-inch needle for lean patients and a 2-inch needle for patients with more SC tissue overlying the gluteal muscle
- Administer XR-NTX every 4 weeks or once a month as a **380 mg IM** gluteal injection
- Alternate buttocks

Follow-up after first dose

- Examine within one week of administering first XR-NTX dose
- Arbitrary time limits on XR-NTX are inappropriate
- Patients who miss a dose can restart their medication after an adequate period of opioid abstinence of 7-14 days

Sources: https://online.lexi.com | https://store.samhsa.gov/sites/default/files/SAMHSA_Digital_Download/PEP21-02-01-002.pdf
https://www.asam.org/quality-care/clinical-guidelines/national-practice-guideline

Discontinuation / Tapering

Signs that the patient may be ready to discontinue

- Sustaining illicit drug abstinence over time
- Stable housing and income
- No legal problems
- Having substantially reduced craving
- Attending counseling or mutual help-groups

Explore buprenorphine or methadone treatment with the patient

- Discourage patients who are not yet stable from discontinuing treatment, because of the high rate of return to illicit opioid use and the increased chance of OD death
- Provide naloxone
- If transitioning to either buprenorphine **or** methadone, begin treatment ~1 day and ~28 days following the last dose of oral naltrexone or IM naltrexone, respectively

Rapid Naltrexone Induction

As an alternative to medically supervised withdrawal, **consider rapid induction in specialty addiction treatment programs**, not general medical settings.

- Delay to treatment initiation with abstinence is challenging
- Patients can successfully initiate XR-NTX in a general outpatient medical setting if they have been **abstinent for sufficient time and pass the naloxone challenge** or started taking XR-NTX elsewhere and are **due for their next injection**

Sources: https://pubmed.ncbi.nlm.nih.gov/22404717/ | https://pubmed.ncbi.nlm.nih.gov/19821290/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5411308/ https://www.asam.org/quality-care/clinical-guidelines/national-practice-guideline

Oral Naltrexone in OUD

Effectiveness is limited due to poor adherence and requirement of 7-14 days of opioid abstinence prior to initiation.

- Lower patient retention compared to oral naltrexone with methadone
- Blocks opioid-induced euphoria for only a day or two. When patients stop taking oral naltrexone, risk of return to opioid use and overdose increase
- **Oral naltrexone may be appropriate in the following circumstances:**
  - Patients who cannot afford XR-NTX but wish to take an antagonist
  - Patients with high level of monitoring and negative consequences for nonadherence
  - Patients leaving controlled environment
- Patients who have taken methadone or extensively used heroin are especially poor oral naltrexone candidates
- SAMHSA TIP panel does not recommend that payers require patients to fail oral before giving IM given the risk of unintentional OD death

Dosing Oral Naltrexone

- Complete the naloxone challenge
- **First dose is 25 mg** (helps reduce risk of precipitated opioid withdrawal compared to full 50 mg and reduce nausea)
  - Dose can be **increased to 50 mg** on the second day
- Increase adherence by observing administration of oral naltrexone
- Sometimes daily 50 mg doses are switched to 3 days per week regimen for a total weekly dose of 350 mg
- ***If patients continue to test the blockade, immediately discuss alternative treatments***

Sources: https://online.lexi.com | https://www.ncbi.nlm.nih.gov/books/NBK541393/
https://store.samhsa.gov/sites/default/files/SAMHSA_Digital_Download/PEP21-02-01-002.pdf

Assessment Question #3

What is the role of an opioid receptor antagonist in treating opioid use disorder?

A. Blocks euphoric effects of opioids through cross-tolerance

B. Blocks euphoric effects of opioids through opioid receptor occupancy

C. Causes no opioid effects

D. A & C

E. B & C

Assessment Question #3

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C. Causes no opioid effects

D. A & C

E. B & C

NALTREXONE SUMMARY

- Naltrexone is a competitive mu-opioid receptor antagonist that blocks effects of opioids and causes no opioid effects
- Patient must be in opioid withdrawal or pass naloxone challenge before initiation to avoid precipitated withdrawal
- The injection formulation XR-NTX (**typical injection dose is 380 mg/4 weeks or 380 mg/1 month**) is preferred over oral naltrexone **(typical oral dose is 50 mg/day**) due to adherence
- Lack of adherence can lead to increased risk of relapse and overdose
- Rapid naltrexone induction may improve patient adherence and prevent patient relapse with naltrexone initiation
- Naltrexone is also approved for alcohol use disorder and may be useful in patients with comorbidities
- Naltrexone cannot be used in pregnancy and has limitations in use for patients with hepatic dysfunction or moderate-to-severe renal impairment
- There is less evidence to support use in OUD compared to methadone and buprenorphine but has fewer drug interactions in comparison
- Consider alternative OUD treatments if patients continue to test the opioid blockade with naltrexone
- Pain management for patients on naltrexone can be challenging

BUPRENOPRHINE

Buprenorphine Overview

Buprenorphine is effective in retaining patients in treatment and reducing illicit opioid use (clinical trials comparing buprenorphine with placebo or no medication). Goal of treatment is full remission from OUD.

It is also shown to have comparable efficacy to methadone.

- It is a partial agonist with a ceiling effect on opioid activity. This property contributed to the decision that buprenorphine can be prescribed to treat OUD outside of OTPs
- A lethal overdose is possible in opioid-naive individuals or when taken in combination with CNS depressants
- DATA 2000 applies to buprenorphine only for OUD; transmucosal buprenorphine is available through pharmacies (outside of OTPs)
    - DATA 2000 does not apply to buprenorphine used to treat pain

- OTPs may administer or dispense buprenorphine, but only providers with SAMHSA waivers can prescribe buprenorphine for OUD
- Switching transmucosal formulations may lead to clinically significant plasma concentration changes that require dose adjustments

Sources: https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2760032 | https://online.lexi.com
https://store.samhsa.gov/sites/default/files/SAMHSA_Digital_Download/PEP21-02-01-002.pdf

Buprenorphine Medication Formulations

Transmucosal / Sublingual

- Flexible dosing, film/buccal strengths come in 75, 150, 300, 450, 600, and 750 mcg; sublingual tablet strengths come in 2 and 8 mg
- 2013 and 2014 branded formulations have greater bioavailability than Suboxone thus achieving the same effect as the original product with lower doses
- **Note:** 5.7 mg/1.4 mg of Zubsolv provides the same buprenorphine exposure as 8 mg/2 mg Suboxone

Implants

- Maintenance treatment for those with clinical stability; patient not taking more than 8 mg of Suboxone or generic equivalents
- 4 rods containing 74.2 mg of buprenorphine each; each rod is effective for 6 months

Injectable

- ER injectable given monthly for moderate to severe OUD treatment among patients who initiated treatment with transmucosal buprenorphine, followed by at least 7 days of dose adjustment
- Available in 300 mg/1.5 mL and 100 mg/0.5 mL formulations as prefilled syringes
- Recommended that the first two monthly doses (300 mg each) are followed by a 100 mg SC monthly maintenance dose
- After discontinuation, patients may have detectable plasma levels of buprenorphine for 12+ months, but duration of detection in urine is not known

Sources: https://store.samhsa.gov/sites/default/files/SAMHSA_Digital_Download/PEP21-02-01-002.pdf | https://www.asam.org/quality-care/clinical-guidelines/national-practice-guideline

Buprenorphine Pharmacology

MOA	• Opioid receptor partial agonist; through cross tolerance and mu-opioid receptor occupancy, at adequate doses, buprenorphine reduces opioid withdrawal and cravings + blunts the effects of illicit opioids • Has high receptor affinity, binds tightly to the mu opioid receptor, prevents other opioids with lower affinity, such as heroin, from binding • It has less potential to cause respiratory depression, given its ceiling effect because it is a partial agonist • Addition of naloxone decreases buprenorphine's potential for misuse
Drug Classification	Schedule III Controlled Medication
Dosing	4 - 24 mg/day or equivalent
Pharmacokinetics	• Wide individual variability • Mean time to maximum plasma concentration is from 40 min to 3.5 hours, so after providing the first dose, wait 2 hours to decide if a second is necessary • Ratio of buprenorphine: naloxone varies across all products, as the absorption of both active ingredients is different for buccal/sublingual films/tablets • If crushed or dissolved for intranasal or IV misuse, both medications are bioavailable, and naloxone blunts immediate opioid agonist effects of buprenorphine • Naloxone will induce opioid withdrawal in people who are physically dependent on opioids • Highly plasma bound, high lipid solubility • Excreted in urine and feces • One active metabolite: norbuprenorphine

Sources: https://online.lexi.com | https://store.samhsa.gov/sites/default/files/SAMHSA_Digital_Download/PEP21-02-01-002.pdf

Buprenorphine Pharmacology

Contraindications	• Allergy to buprenorphine, allergy to naloxone (infrequent), current physiological dependence

Precautions/ Warnings	• Respiratory depression/OD are uncommon in adults, but they do happen; pediatric exposure can be fatal
	• Cases of hepatitis and liver failure exist but often involve predisposing hepatic risk factors
	• Potential for misuse and diversion (B/N transmucosal products are abuse-deterrent formulations but can still be misused)
	• Can misuse via intranasal or IV routes or divert it for others to misuse
	• Adrenal insufficiency has been reported, often after more than 1 month of buprenorphine maintenance
	• Patients will develop physical dependence on buprenorphine (risk of opioid withdrawal)
	• May affect cognition/psychomotor performance and cause sedation, especially in those who have lost tolerance to opioids after a period of abstinence
	• **Can cause precipitated opioid withdrawal**, it has weaker opioid agonist effects and stronger receptor affinity than full agonists, such as heroin and methadone. It can displace these full agonists and precipitate opioid withdrawal. **Factors affecting this include**:
	  • Current level of opioid physical dependence
	  • Time since last mu-opioid receptor full agonist dose
	  • Dose of buprenorphine
	• NAS may occur in newborns of pregnant women who take buprenorphine
	  • Dose is not related to severity of NAS; not all babies born to women treated with opioid agonists require treatment for NAS
	• Signs of withdrawal may be relieved if necessary with short-term use of additional low doses of transmucosal buprenorphine

Sources: https://online.lexi.com | https://store.samhsa.gov/sites/default/files/SAMHSA_Digital_Download/PEP21-02-01-002.pdf
https://www.asam.org/quality-care/clinical-guidelines/national-practice-guideline

Buprenorphine Pharmacology

Side effects	Oral numbness, constipation, tongue pain, oral mucosal erythema, vomiting, intoxication, disturbance in attention, palpitations, insomnia, opioid withdrawal syndrome, excessive sweating, blurred vision

Drug interactions	• Fewer documented clinically significant drug interactions than methadone; FDA warns on increased serotonin syndrome risk with use of prescription opioids including buprenorphine
	• Monitoring needed for patients starting/stopping drugs that are 3A4 inhibitors/inducers as oversedation or withdrawal may result
	  • **Inducers:** Carbamazepine, phenobarbital, phenytoin, primidone, rifampin, dexamethasone
	  • **Inhibitors:**
	  • **Analgesics**: fentanyl
	  • **Antiarrhythmics**: amiodarone, disopyramide, quinidine
	  • **Antibiotics**: rifampin, clarithromycin, clindamycin, erythromycin
	  • **Antidepressants**: fluoxetine, fluvoxamine, nefazodone
	  • **Antifungals**: fluconazole, itraconazole, ketoconazole, miconazole
	  • **Antihistamines**: loratadine
	  • **Antihypertensives**: amlodipine, diltiazem, felodipine, nicardipine, nifedipine, nimodipine, verapamil
	  • **Antineoplastics**: doxorubicin, etoposide, ifosfamide, paclitaxel, vinblastine
	  • **Gastric agents**: aprepitant, cimetidine
	  • **Hormones**: estrogen, oral contraceptives, progestins
	  • **Immune suppressants**: cyclosporine, dexamethasone, zafirlukast
	  • **Sedatives/Hypnotics**: alprazolam, clonazepam, diazepam, midazolam
	  • **Statins**: atorvastatin, lovastatin, simvastatin
	  • Warfarin
	• Monitor responses to buprenorphine in patients taking **NRTIs** or **combination antiretroviral therapy**, as well as **TB treatment**
	• More drug interaction concerns with depot formulation

Sources: https://online.lexi.com | https://store.samhsa.gov/sites/default/files/SAMHSA_Digital_Download/PEP21-02-01-002.pdf
https://www.asam.org/quality-care/clinical-guidelines/national-practice-guideline

Assessment Question #4

A potential concern with using calcium channel blockers such as verapamil concurrently with buprenorphine is:

A. Decreased buprenorphine serum levels through inhibition of CYP450

B. Decreased buprenorphine serum levels through induction of CYP450

C. Increased buprenorphine serum levels through inhibition of CYP450

D. Increased buprenorphine serum levels through induction of CYP450

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Buprenorphine Induction Settings

Office-based Induction

- Order and store induction doses in the office or by prescribing medication and instructing patients to bring it to the office on the day of induction
- Allows providers to ensure patients know how to take medications, enhance relationship, verify presence of opioid withdrawal and absence of precipitated withdrawal, ensure lack of sedation after first dose, use time between doses for patient self assessment

Home Induction

- The American Society of Addiction Medicine recommends home induction only if the patient/prescriber has experience with buprenorphine
- Educate patients on how to assess withdrawal, when to start first dose, take medication properly, and how to manage withdrawal on induction day
    - Take induction dose at least 12 hours after last heroin use or short-acting prescription opioid
- Advise patients to abstain from tobacco before dosing generally
- See patients 7 days after the start of home induction

Sources: https://www.ncbi.nlm.nih.gov/books/NBK64245/pdf/Bookshelf_NBK64245.pdf | https://store.samhsa.gov/sites/default/files/SAMHSA_Digital_Download/PEP21-02-01-002.pdf
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Initiating & Maintaining Buprenorphine Treatment

Induction for patients who are currently physically dependent on opioids

- Should begin buprenorphine when they are exhibiting clear signs of opioid withdrawal
  - Can **start with a 2 - 4 mg** dose of buprenorphine or 2 mg/0.5 mg or 4 mg/1 mg dose of combination buprenorphine/naloxone
  - The dose can take between 3 - 10 minutes to dissolve fully
  - After 2 hours, **another 2 - 4 mg can be given** if there is continued withdrawal and lack of sedation
- Always individualized dosing: **maximum of 8 mg on day 1 and 16 mg on day 2**
- If the patient experiences sedation upon first dose, stop and reevaluate
- Consider dose decrease and/or change in treatment plan. If induction is still indicated, adjust the dose more slowly to minimize sedation

Induction for patients who are NOT currently physically dependent on opioids

- Buprenorphine doses should begin at lower-than–usual levels (**1 mg**) and increased more slowly than in tolerant patients to avoid oversedation and possible overdose. Caution with use alongside other CNS depressants
- Directly administer doses to patients in an OTP or in office, to be observed for sedation
- Common strategy: 1 mg with weekly 1 mg doses increases to 4 mg, followed by 2 mg weekly increases to 8 mg
- The mean daily dose should exceed 8 mg per day by the fifth week

Sources: https://www.ncbi.nlm.nih.gov/books/NBK64245/pdf/Bookshelf_NBK64245.pdf | https://store.samhsa.gov/sites/default/files/SAMHSA_Digital_Download/PEP21-02-01-002.pdf
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Initiating & Maintaining Buprenorphine Treatment

Induction for patients who are currently taking methadone

- Must taper methadone (30 - 40 mg/day and stay on dose for at least 1 week) prior to initiating buprenorphine
- Do not start buprenorphine until the patient manifests signs of opioid withdrawal
  - Wait 24 hours between the last methadone dose and the first buprenorphine dose
  - Waiting 36+ hours reduces risk of precipitated withdrawal
  - Lower doses of buprenorphine/naloxone are less likely to precipitate methadone withdrawal
  - Once opioid withdrawal is verified, an **initial dose of 2 mg/0.5 mg** can be given
    - If patients continue to have unrelieved opioid withdrawal after the first 2 mg dose, administer another 2 mg/0.5 mg approximately every 2 hours as needed (holding for sedation)
    - Induction should be conducted slowly, and the patient should be monitored for precipitated withdrawal

Once dose stabilization occurs

- Remind patients to take their dose once daily rather than splitting it
- Continue monitoring dose effectiveness during early stabilization as dose adjustments may still be necessary
- Once stabilized, continue to screen and evaluate for mental disorders/psychosocial problems that need to be addressed, offer referrals for adjunctive counseling and recovery support services as needed
- Be cautious when increasing doses above 24 mg/6 mg per day. Nearly all patients stabilize to 4 - 24 mg. Higher doses may unintentionally heighten diversion risk. Patients not responding to high doses of buprenorphine should be considered for methadone treatment

Sources: https://www.ncbi.nlm.nih.gov/books/NBK64245/pdf/Bookshelf_NBK64245.pdf | https://store.samhsa.gov/sites/default/files/SAMHSA_Digital_Download/PEP21-02-01-002.pdf
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Initiating & Maintaining Buprenorphine Treatment

Transitioning to subcutaneous injections

- Healthcare settings and pharmacies need special certification to order/dispense ER injectable buprenorphine to ensure that they are dispensed directly to HCPs for administration to patients
- **Patients should be stabilized on TM buprenorphine 8 - 24 mg daily for at least 7 days prior to initiating the injection**
- Should not be used in opioid naive patients and there is insufficient data for use in pregnancy
- Usually stored in the refrigerator. Keep at room temperature for ≥15 minutes before administration. Discard if left at room temperature for >7 days
- Administration: abdominal SC , rotate with each injection
- Each of the **first two monthly doses should be 300 mg** (with at least 26 days between doses); **subsequent doses should be 100 mg**
    - Some patients may benefit increasing to 300 mg monthly if they have tolerated 100 mg but continue to use illicit opioids

Transitioning to depot implants

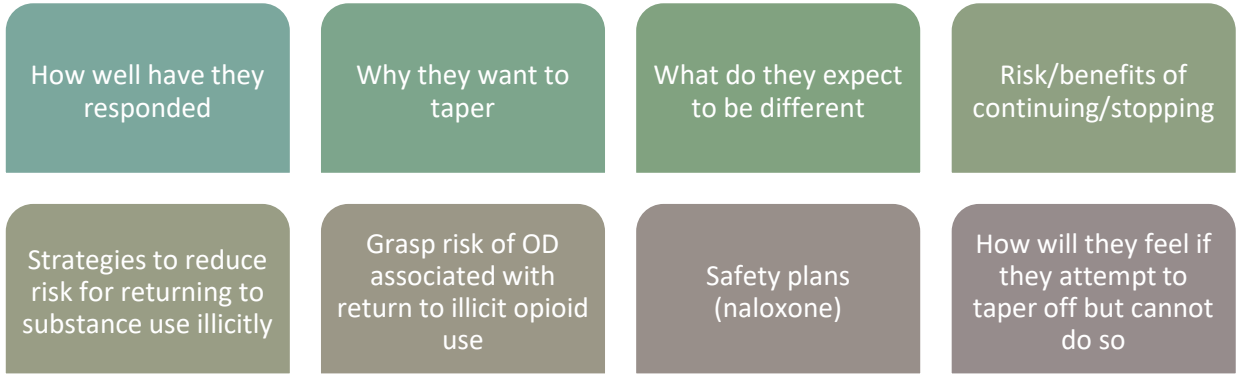
- **Patients need to be taking no more than 8 mg of Suboxone or generic equivalents**
- Prescribers and implanters require special certification to make this formulation available to patients
- **Instruct the patients to take the last TM dose of buprenorphine 12 - 24 hours before insertion**. Remind them to shower and thoroughly wash the nondominant arm, which is preferred for insertion
- Return within 1 week after the implant procedure to check for wound care. Once stabilized, schedule office visits no less than once a month for continued assessment. After 6 months, remove and implant the other one in the opposite arm
- Consider transmucosal medication supplements if a patient with implants destabilizes

Sources: https://www.ncbi.nlm.nih.gov/books/NBK64245/pdf/Bookshelf_NBK64245.pdf | https://store.samhsa.gov/sites/default/files/SAMHSA_Digital_Download/PEP21-02-01-002.pdf
https://www.asam.org/quality-care/clinical-guidelines/national-practice-guideline

Discontinuation / Tapering Buprenorphine

Following short-term medically supervised withdrawal, patients frequently restart illicit opioid use (gradually reducing the dose of buprenorphine).

- Decisions to decrease dose or stop buprenorphine should be based on the patient's situation. It is up to patients to decide, but before tapering, explore:



- There is **no ideal tapering protocol,** but it is a slow process and is generally accomplished over several months with a gradual dose reduction; ancillary medications may be used.
- Patients who successfully taper off buprenorphine completely (7 - 14 days) could potentially switch to naltrexone (with naloxone challenge)
- Patients who choose to switch from buprenorphine to methadone therapy can do so without delay

Sources: https://www.ncbi.nlm.nih.gov/books/NBK64245/pdf/Bookshelf_NBK64245.pdf | https://store.samhsa.gov/sites/default/files/SAMHSA_Digital_Download/PEP21-02-01-002.pdf
https://www.asam.org/quality-care/clinical-guidelines/national-practice-guideline

BUPRENORPHINE SUMMARY

- Buprenorphine is a partial mu-opioid receptor agonist with a ceiling effect (negated with concurrent benzodiazepine or alcohol use) that limits opioid adverse effects such as respiratory depression and euphoria
- Buprenorphine is shown to lower overdose mortality and suppress illicit opioid use and has a high retention rate
- Patient must be in opioid withdrawal or pass naloxone challenge before initiation to avoid precipitated withdrawal
- Can come in a combination product with naloxone to deter diversion and abuse, has flexible dosing
- **Typical first dose with TM formulations is 2 mg/0.5 mg - 4 mg/1 mg** and the dose should be repeated up to 8 mg total on the first day
- **Maintenance dose is typically 4 mg/1 mg - 24 mg/6 mg per day** and is the lowest dose for the patient that can eliminate withdrawal without sedation
- Buprenorphine can be initiated in the outpatient setting (OBOTs or home-induction) and in the ED setting, but an X-waiver is required to prescribed buprenorphine to treat OUD. EDs can adhere to the 3-day rule for buprenorphine initiation without an X-wavier while arranging a referral
- The buprenorphine monoproduct can be used in pregnant women
- Has fewer drug interactions than methadone, but most concerns are with precipitated opioid withdrawal and long-acting formulations
- Switching to the injection formulation or the implant requires specific criteria related to the patient being stable on the transmucosal formulation

PATIENT CASE

JC is a 43 y/o male with HTN, HLD, depression, and a recent hip replacement (~6 months ago) is admitted into the ED after a hypertensive crisis (BP = 192/130 mmHg).

- He is taking valsartan 80 twice daily, hydrochlorothiazide 25 mg once daily, atorvastatin 20 mg once daily, and venlafaxine 75 mg once daily. He shares that he had taken all of his PRN oxycodone IR 10 mg after his hip procedure and that when he stopped taking his pain medications once he ran out, he felt like he couldn't stop taking them. Recently, he has been trying to find pain medications around the house and goes around asking family members if they have any to supply to him. He reports that he was taking them consistently until about two days ago.

- Upon receiving treatment with IV antihypertensives, his blood pressure has been stabilized but he is still showing signs and symptoms of sweating, vomiting, piloerection, and pupil dilation.

- It has been determined that the patient is currently in opioid withdrawal and meets DSM5 diagnosis criteria for OUD. He has a COWS score of 10.

What would be the next step in his management in the hospital?

PATIENT CARE PLAN

- **Educate the patient on OUD treatment and transition him to maintenance treatment with buprenorphine/naloxone.**
  - Patient is already exhibiting clear signs of opioid withdrawal
  - Provide ancillary medications such as ondansetron as necessary
  - Initiate 4 mg/1 mg of buprenorphine/naloxone and monitor for sedation and withdrawal symptoms for the next 2 hours
  - After the 2 hours, another 4 mg/1 mg of buprenorphine/naloxone can be given again (max first daily dose is 8 mg)
  - The patient should be titrated to a stable dose in which he no longer experiences withdrawal symptoms or sedation

- **Refer the patient for additional psychosocial treatment, recovery support services at discharge.**
  - Provide additional education on treatment options; allow for informed consent with continued treatment
  - Connect the patient with community resources and refer the patient to an OBOT if he is interested

KEY OUD MEDICATIONS SUMMARY

OUD medications are safe and effective when used appropriately.

OUD medications can help patients reduce or stop illicit opioid use and improve their health and functioning.

Medication should be considered for all patients with OUD.

Reserve opioid pharmacotherapies for those with moderate-to-severe OUD with physical dependence.

Patients with OUD should be informed of the risks and benefits of medication, treatment without medication, and no treatment.

Patients should be advised on where and how to get treatment with OUD medication.

Doses and schedules of medication for OUD must be individualized.

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Thank you!

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