The course below counts as two hours toward the 8-hour DEA requirement for Medication Access and Training Expansion Course (MAATE)

A two hour course on those drugs approved by FDA for the treatment of a substance use disorder

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Beginning in June, 2023, dentists will be required to check a box on their online DEA registration form – regardless of whether a registrant is completing their initial registration application or renewing their registration – affirming that they have completed a new **one-time eight-hour** training requirement. The deadline for satisfying the requirement is the date of a practitioners' next scheduled DEA registration submission on or after June 27, 2023. This present course provides two of the eight hours of the requirement.

The course follows the Clinical Practice Guidelines from the American Society of Addiction Medicine for the drugs used in opiate use disorder as of 2020. The course opens with a short summary of the rationale for medications in opioid withdrawal including opioid agonists and alpha-2 adrenergic agonists. Then the bulk of the course describes the three major drugs for treatment- methadone, buprenorphine and naltrexone. For each agent the following will be presented – background for use, mechanism of action at molecular level, precautions in use, dose initiation to dose titration to doses for maintenance, adverse effects, course of treatment, length of treatment, monitoring treatment, drug formulations, treatment access issues and required physician qualifications. The role of naloxone in buprenorphine formulation (Suboxone) will be discussed. Finally, issues relative to transitions between medications will be described (methadone to buprenorphine, methadone to naltrexone, buprenorphine to naltrexone, buprenorphine to methadone).

After completing the course, the participants will be able to:

- Describe the rationale for using opiate medications in opioid withdrawal
- Name the three major drugs used to treat opioid use disorder
- For the drugs named above, describe its mechanism of action, key adverse effects and drug formulations
- Describe the role of naloxone in the buprenorphine formulation (Suboxone).
- Describe the requirements for physicians to prescribe Suboxone in Office-based Opioid Treatment (OBOT). Also, the latest methadone/buprenorphine rule as of April 2024.
- List ten symptoms of opiate withdrawal.

Substances: Category and Name	Examples of *Commercial* and Street Names	DEA Schedule*/ How Administered**	*Intoxication Effects*/Potential Health Consequences
Cannabinoids			
hashish	boom, chronic, gangster, hash, hash oil, hemp	I/swallowed, smoked	*euphoria, slowed thinking and reaction time, confusion, impaired balance and coordination*; cough, frequent respiratory infections; impaired memory and learning; increased heart rate, anxiety; panic attacks; tolerance, addiction
marijuana	blunt, dope, ganja, grass, herb, joints, Mary Jane, pot, reefer, sinsemilla, skunk, weed	I/swallowed, smoked	
Depressants			
barbiturates	*Amytal, Nembutal, Seconal, Phenobarbital:* barbs, reds, red birds, phennies, tooies, yellows, yellow jackets	II, III, V/injected, swallowed	*reduced anxiety; feeling of well-being; lowered inhibitions; slowed pulse and breathing; lowered blood pressure; poor concentration*/fatigue; confusion impaired coordination, memory, judgment; addiction; respiratory depression and arrest, death ***Also, for barbiturates—sedation, drowsiness/depression,*** unusual excitement, fever, irritability, poor judgment, slurred speech, dizziness, life-threatening withdrawal
benzodiazepines (other than flunitrazepam)	*Ativan, Halcion, Librium, Valium, Xanax:* candy, downers, sleeping pills, tranks	IV/swallowed, injected	
flunitrazepam***	*Rohypnol:* forget-me pill, Mexican Valium, R2, Roche, roofies, roofinol, rope, rophies	IV/swallowed, snorted	***for benzodiazepines—sedation, drowsiness/dizziness*** ***for flunitrazepam***—visual and gastrointestinal disturbances, urinary retention, memory loss for the time under the drug's effects
GHB***	*gamma-hydroxybutyrate:* G, Georgia home boy, grievous bodily harm, liquid ecstasy	I/swallowed	***for GHB***—drowsiness, nausea/vomiting, headache, loss of consciousness, loss of reflexes, seizures, coma, death

Dissociative Anesthetics			*increased heart rate and blood pressure, impaired motor function*/memory loss; numbness; nausea/vomiting *Also, for ketamine—at high doses, delirium, depression, respiratory depression and arrest*
ketamine	*Ketalar SV:* cat Valiums, K, Special K, vitamin K	III/injected, snorted, smoked	
PCP and analogs	*phencyclidine;* angel dust, boat, hog, love boat, peace pill	I, II/injected, swallowed, smoked	*for PCP and analogs—possible decrease in blood pressure and heart rate, panic, aggression, violence*/loss of appetite, depression
Hallucinogens			*altered states of perception and feeling; nausea*; persisting perception disorder (flashbacks)
LSD	*lysergic acid diethylamide:* acid, blotter, boomers, cubes, microdot, yellow sunshines	I/swallowed, absorbed through mouth tissues	*Also, Also for LSD and mescaline—increased body temperature, heart rate, blood pressure; loss of appetite, sleeplessness, numbness, weakness, tremors* *for for LSD—persistent mental disorders*
mescaline	buttons, cactus, mesc, peyote	I/swallowed, smoked	
psilocybin	magic mushroom, purple passion, shrooms	I/swallowed	*for for psilocybin—nervousness, paranoia*

Supplemental Slide

Opioids and Morphine Derivatives			
codeine	*Empirin with Codeine, Fiorinal with Codeine, Robitussin A-C, Tylenol with Codeine:* Captain Cody, schoolboy; (with glutethimide) doors & fours, loads, pancakes and syrup	II, III, IV, V/injected, swallowed	*pain relief, euphoria, drowsiness*/nausea, constipation, confusion, sedation, respiratory depression and arrest, tolerance, addiction, unconsciousness, coma, death *Also, for codeine—less analgesia, sedation, and respiratory depression than morphine* *for heroin—staggering gait*
fentanyl and fentanyl analogs	*Actiq, Duragesic, Sublimaze:* Apache, China girl, China white, dance fever, friend, goodfella, jackpot, murder 8, TNT, Tango and Cash	I, II/injected, smoked, snorted	
heroin	*diacetyl-morphine:* brown sugar, dope, H, horse, junk, skag, skunk, smack, white horse	I/injected, smoked, snorted	
morphine	*Roxanol, Duramorph:* M, Miss Emma, monkey, white stuff	II, III/injected, swallowed, smoked	
opium	*laudanum, paregoric:* big O, black stuff, block, gum, hop	II, III, V/swallowed, smoked	
oxycodone HCL	*Oxycontin:* Oxy, O.C., killer	II/swallowed, snorted, injected	
hydrocodone bitartrate, acetaminophen	*Vicodin:* vike, Watson-387	II/swallowed	

Supplemental Slide

Stimulants			
amphetamine	*Biphetamine, Dexedrine:* bennies, black beauties, crosses, hearts, LA turnaround, speed, truck drivers, uppers	II/injected, swallowed, smoked, snorted	*increased heart rate, blood pressure, metabolism; feelings of exhilaration, energy, increased mental alertness*/rapid or irregular heart beat; reduced appetite, weight loss, heart failure, nervousness, insomnia *Also, for amphetamine—rapid breathing*/tremor, loss of coordination; irritability, anxiousness, restlessness, delirium, panic, paranoia, impulsive behavior, aggressiveness, tolerance, addiction, psychosis
cocaine	*Cocaine hydrochloride:* blow, bump, C, candy, Charlie, coke, crack, flake, rock, snow, toot	II/injected, smoked, snorted	*for cocaine—increased temperature*/chest pain, respiratory failure, nausea, abdominal pain, strokes, seizures, headaches, malnutrition, panic attacks
MDMA (methylenedioxy-methamphetamine)	Adam, clarity, ecstasy, Eve, lover's speed, peace, STP, X, XTC	I/swallowed	*for MDMA—mild hallucinogenic effects, increased tactile sensitivity, empathic feelings*/impaired memory and learning, hyperthermia, cardiac toxicity, renal failure, liver toxicity
methamphetamine	*Desoxyn:* chalk, crank, crystal, fire, glass, go fast, ice, meth, speed	II/injected, swallowed, smoked, snorted	*for methamphetamine—aggression, violence, psychotic behavior*/memory loss, cardiac and neurological damage; impaired memory and learning, tolerance, addiction
methylphenidate (safe and effective for treatment of ADHD)	*Ritalin:* JIF, MPH, R-ball, Skippy, the smart drug, vitamin R	II/injected, swallowed, snorted	*for nicotine*—additional effects attributable to tobacco exposure; adverse pregnancy outcomes; chronic lung disease, cardiovascular disease, stroke, cancer, tolerance, addiction
nicotine	cigarettes, cigars, smokeless tobacco, snuff, spit tobacco, bidis, chew	not scheduled/smoked, snorted, taken in snuff and spit tobacco	

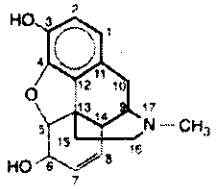
Supplemental Slide

Other Compounds

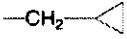
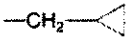
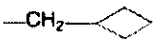
anabolic steroids	*Anadrol, Oxandrin, Durabolin, Depo-Testosterone, Equipoise:* roids, juice	III/injected, swallowed, applied to skin	*no intoxication effects*/hypertension, blood clotting and cholesterol changes, liver cysts and cancer, kidney cancer, hostility and aggression, acne; in adolescents, premature stoppage of growth; in males, prostate cancer, reduced sperm production, shrunken testicles, breast enlargement; in females, menstrual irregularities, development of beard and other masculine characteristics
Dextromethorphan (DXM)	*Found in some cough and cold medications; Robotripping, Robo, Triple C*	not scheduled/swallowed	*Dissociative effects, distorted visual perceptions to complete dissociative effects*/for effects at higher doses see 'dissociative anesthetics'
inhalants	*Solvents (paint thinners, gasoline, glues), gases (butane, propane, aerosol propellants, nitrous oxide), nitrites (isoamyl, isobutyl, cyclohexyl):* laughing gas, poppers, snappers, whippets	not scheduled/inhaled through nose or mouth	*stimulation, loss of inhibition; headache; nausea or vomiting; slurred speech, loss of motor coordination; wheezing*/unconsciousness, cramps, weight loss, muscle weakness, depression, memory impairment, damage to cardiovascular and nervous systems, sudden death

Supplemental Slide

Table 21–5
Structures of Opioids and Opioid Antagonists Chemically Related to Morphine



MORPHINE

	RADICALS AND POSITION*			
	3	6	17	Other Changes†
Morphine	—OH	—OH	—CH_3	—
Heroin	—$OCOCH_3$	—$OCOCH_3$	—CH_3	—
Hydromorphone	—OH	=O	—CH_3	(1)
Oxymorphone	—OH	=O	—CH_3	(1), (2)
Levorphanol	—OH	—H	—CH_3	(1), (3)
Levallorphan	—OH	—H	—$CH_2CH{=}CH_2$	(1), (3)
Codeine	—OCH_3	—OH	—CH_3	—
Hydrocodone	—OCH_3	=O	—CH_3	(1)
Oxycodone	—OCH_3	=O	—CH_3	(1), (2)
Nalmefene	—OH	$=CH_2$	—CH_2— 	(1), (2)
Nalorphine	—OH	—OH	—$CH_2CH{=}CH_2$	—
Naloxone	—OH	=O	—$CH_2CH{=}CH_2$	(1), (2)
Naltrexone	—OH	=O	—CH_2— 	(1), (2)
Buprenorphine	—OH	—OCH_3	—CH_2— 	(1), (4)
Butorphanol	—OH	—H	—CH_2— 	(1), (2), (3)
Nalbuphine	—OH	—OH	—CH_2— 	(1), (2)

*The numbers 3, 6, and 17 refer to positions in the morphine molecule, as shown above. †Other changes in the morphine molecule are: (1) Single instead of double bond between C7 and C8; (2) OH added to C14; (3) No oxygen between C4 and C5; (4) *Endo*etheno bridge between C6 and C14; 1-hydroxy-1,2,2-trimethylpropyl substitution on C7.

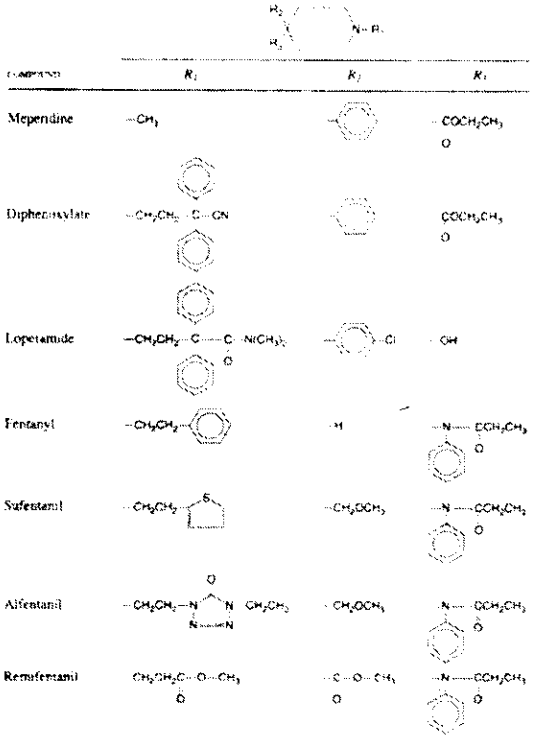


Figure 21–4. *Chemical structures of piperidine and phenylpiperidine analgesics.*

Absorption, Fate, and Excretion. Meperidine is absorbed by all routes of administration, but the rate of absorption may be erratic after intramuscular injection. The peak plasma concentration usually occurs at about 45 minutes, but the range is wide. After oral administration, only about 50% of the drug escapes first pass metabolism to enter the circulation, and peak concentrations in plasma usually are observed in 1 to 2 hours.

In humans, meperidine is hydrolyzed to meperidinic acid, which, in turn, is partially conjugated. Meperidine also is N-demethylated to normeperidine, which then may be hydrolyzed to normeperidinic acid and subsequently

Major pathways in full mode - Symptoms

- Pain, sickness
- Flu-like feeling
- Insomnia
- Stomach cramps, nausea
- Sweating
- Psychological disturbances, etc
- Unbearable need for next fix

Characteristics of Medications for Opioid-Addiction Treatment.

Characteristic	Methadone	Buprenorphine	Naltrexone
Brand names	Dolophine, Methadose	Subutex, Suboxone, Zubsolv	Depade, ReVia, Vivitrol
Class	Agonist (fully activates opioid receptors)	Partial agonist (activates opioid receptors but produces a diminished response even with full occupancy)	Antagonist (blocks the opioid receptors and interferes with the rewarding and analgesic effects of opioids)
Use and effects	Taken once per day orally to reduce opioid cravings and withdrawal symptoms	Taken orally or sublingually (usually once a day) to relieve opioid cravings and withdrawal symptoms	Taken orally or by injection to diminish the reinforcing effects of opioids (potentially extinguishing the association between conditioned stimuli and opioid use)
Advantages	High strength and efficacy as long as oral dosing (which slows brain uptake and reduces euphoria) is adhered to; excellent option for patients who have no response to other medications	Eligible to be prescribed by certified physicians, which eliminates the need to visit specialized treatment clinics and thus widens availability	Not addictive or sedating and does not result in physical dependence; a recently approved depot injection formulation, Vivitrol, eliminates need for daily dosing
Disadvantages	Mostly available through approved outpatient treatment programs, which patients must visit daily	Subutex has measurable abuse liability; Suboxone diminishes this risk by including naloxone, an antagonist that induces withdrawal if the drug is injected	Poor patient compliance (but Vivitrol should improve compliance); initiation requires attaining prolonged (e.g., 7-day) abstinence, during which withdrawal, relapse, and early dropout may occur

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Methadone – FDA Use – from professional package insert

1. Opioid withdrawal, short-term medically supervised: Short-term, medically supervised opioid withdrawal, in conjunction with appropriate social and medical services.

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Methadone – FDA Use – from professional package insert

Use

2. Opioid use disorder, maintenance treatment: Maintenance treatment of opioid use disorder, in conjunction with appropriate social and medical services.

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Methadone – FDA Use

3. Pain, chronic:
Injection: Management of pain severe enough to require an opioid analgesic and for which alternative treatment options are inadequate.
Oral: Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
Limitations of use: Reserve for use in patients for whom alternative treatment options (eg, nonopioid analgesics, opioid combination products) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. Dolophine is not indicated for use as an as-needed analgesic.

Dosage Forms: US

Concentrate, Oral, as hydrochloride:
Methadone HCl Intensol: 10 mg/mL (30 mL)
Methadose: 10 mg/mL (1000 mL) cherry flavor]
Methadose Sugar-Free: 10 mg/mL (1000 mL)
Generic: 10 mg/mL (30 mL, 1000 mL)

Solution, Injection, as hydrochloride:
Generic: 10 mg/mL (20 mL)

Solution, Oral, as hydrochloride:
Generic: 5 mg/5 mL (5 mL, 500 mL); 10 mg/5 mL (500 mL)

Tablet, Oral, as hydrochloride:
Generic: 5 mg, 10 mg

Tablet Soluble, Oral, as hydrochloride:
Methadose: 40 mg Diskettes dispersible tabs
Generic: 40 mg

Why Medication Therapy

Once the diagnosis of opioid use disorder has been established, and the patient is determined to be medically and psychiatrically stable, the next task is to decide on a course of treatment. Treatment options include pharmacotherapy with one of three medications – methadone, buprenorphine, or naltrexone – and psychosocial treatment. Withdrawal management alone can be the first step but is not a treatment for opioid use disorder and should only be considered as a part of a comprehensive and longitudinal plan of care.

Behavior change is an important part of recovery, that may be facilitated by psychosocial treatment. However, these treatments take time to be effective. Medications work quickly to reduce the risk for overdose and overdose death. Thus, the combination of pharmacotherapy and psychosocial treatments, tailored to the individual's needs, is the recommended standard of care.

Opioid withdrawal using methadone - short-term medically supervised:

Note: Maintenance treatment with methadone is associated with better outcomes than short-term medically supervised withdrawal.

Reserve medically supervised withdrawal for patients who do not wish to undergo maintenance treatment or who will be transitioning to maintenance treatment with naltrexone (SAMHSA 2021).

Initial: Oral: Titrate to ~40 mg/day in divided doses to achieve stabilization.

Continuation: May continue 40 mg/day dose for 2 to 3 days.

Discontinuation of therapy: After 2 to 3 days at a stable dose, gradually decrease the dose on a daily basis or at 2-day intervals. Keep dose at a level sufficient to keep withdrawal symptoms at a tolerable level. Hospitalized patients may tolerate a total daily dose decrease of 20%; ambulatory patients may require a slower reduction.

Methadone Initiation

Patients with no or low tolerance at initiation (eg, absence of opioids ≥5 days, do not take opioids daily, use of weaker opioids [eg, codeine]): **Oral:** 2.5 to 10 mg (as a single dose) (ASAM 2020; SAMHSA 2021).

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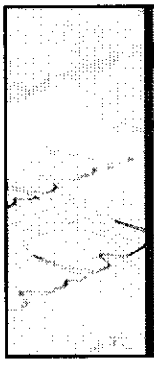

Methadone-Initiation to maintenance dosing

- Patients engaging in problem drinking, those with lower levels of opioid tolerance or individuals with medical conditions that may cause hypoxia, hypercapnia or cardiac arrhythmias (eg, asthma, chronic obstructive pulmonary disease, cor pulmonale, electrolyte abnormalities, family history of cardiac arrhythmias, dizziness or fainting or sudden death, kyphoscoliosis, obesity, QTc prolongation, sleep apnea): **Oral:** 10 to 20 mg (as a single dose) (SAMHSA 2021).

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Methadone - Initiation to maintenance dosing

- **Note:** Regardless of initial dose, observe patients for over-sedation and withdrawal symptoms for 2 to 4 hours after initial dose (ASAM 2020; SAMHSA 2021); an additional 5 to 10 mg orally may be provided if withdrawal symptoms have not been suppressed or if symptoms reappear after 2 to 4 hours; total daily dose on the first day should not exceed 40 mg.

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Methdaone -Maintenance: Oral: Titrate cautiously to a dosage which prevents opioid withdrawal symptoms for 24 hours, prevents craving, attenuates euphoric effect of self-administered opioids, and tolerance to sedative effects of methadone. Some experts recommend increasing by no more than 10 mg every 5 days. Slower titrations such as 5 mg every week should be considered in patients with no or low tolerance at initiation (eg, absence of opioids ≥5 days, do not take opioids daily, use of weaker opioids [eg, codeine]) (ASAM 2020; SAMHSA 2021

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Methadone - if a patient experiences sedation 2 to 4 hours after their last dose and craving or withdrawal prior to the next dose, consider dividing the daily dose into twice daily dosing. If patient experiences relief from withdrawal 4 to 12 hours after their last dose, maintain this dose for a few days so methadone can reach steady state (SAMHSA 2021). Levels will accumulate over the first few days; deaths have occurred in early treatment due to cumulative effects.
Usual range: 60 to 120 mg/day (ASAM 2020).
Missed dose: In patients who miss >4 doses, consider restarting at the initial dose or decrease the next dose substantially and gradually re-titrate (SAMHSA 2021).

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Generic Name	For the Treatment of	Effects	Potential Side Effects	Advantages	Disadvantages
Methadone Methadone	Opioid withdrawal management; Ongoing treatment of opioid use disorder	Improved retention in treatment, reduced withdrawal symptoms and cravings, reduced illicit opioid use, reduced mortality risk	Constipation, hyperhidrosis, respiratory depression (particularly combined with benzodiazepines or other CNS depressants), sedation, QT prolongation, interactions with other medications that alter cytochrome P450 metabolism, sexual dysfunction, severe hypotension including orthostatic hypotension and syncope, misuse potential, NOWS	Strongest retention in treatment; improved social functioning; associated with reductions in criminal activity and recidivism; and infectious disease acquisition and transmission	More frequent clinic visits, only SAMHSA-certified OTPs may provide methadone for addiction treatment, higher risk for respiratory depression due to long half-life and stacking effect (requires more monitoring)

GENERIC/TRADE NAME	MU-OPIOID RECEPTOR EFFECT	FOR THE TREATMENT OF	FORMULATIONS	AVAILABLE STRENGTHS	COMMON MAINTENANCE DOSE	STANDARD DOSING REGIMEN
Methadone (Methadose, Dolophine)	Full agonist	Opioid withdrawal and opioid use disorder	Liquid concentrate, tablet, oral solution of powder or dispersible tablet	tablet: 5 mg, 10mg dispersible tablet: 40mg oral solution: 5mg/5 mL, 10mg/5mL oral concentrate solution: 10mg/mL	Range: 60 to 120 mg	Once daily (or split dosing when appropriate)

Table II: Brand Preparations of Buprenorphine Currently Approved in the US.

Type	Buprenorphine	Buprenorphine/Naloxone	Buprenorphine long-acting
Indication	pain	opioid dependence substitution indication Sublingual	opioid dependence substitution indication
Brands (available doses)	Belbuca (75, 150, 300, 450, 600, 750, or 900 mcg)	Suboxone Film (2/0.5, 4/1, 8/2, or 12/3 mg)	Sublocade injection (100, 300 mg monthly)
	Butrans (5, 7.5, 10, 15, or 20 mcg/h or a 7-day patch)	Zubsolv Tab (0.7/0.18, 1.4/036, 2.9/071, 5.7/1.4, 8.6/2.1, 11.4/2.9 mg)	Probuphine implant (74.2 mg every six months)
	Buprenex (300 mcg/ml via intramuscular or intravenous administration)	~~Bunavail (2.1/0.3, 4.2/0.7, 6.3/1 mg)~~	Brixadi injection (8, 16, 24 or 32 mg weekly; 64, 96, or 128 mg monthly)

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Induction: Day 1 induction dose: Initial: Sublingual: Buprenorphine 2 mg/naloxone 0.5 mg or buprenorphine 4 mg/naloxone 1 mg; consider an initial dose of buprenorphine 1 mg and naloxone 0.25 mg in patients with a history of opioid use disorder with a high risk of relapse but not currently dependent on opioids (Ref). May titrate dose, based on control of acute withdrawal symptoms, in buprenorphine 2 mg/naloxone 0.5 mg or buprenorphine 4 mg/naloxone 1 mg increments approximately every 2 hours up to a total dose of buprenorphine 8 mg/naloxone 2 mg (Ref).

Day 2 induction dose: Sublingual: Up to buprenorphine 16 mg/naloxone 4 mg as a single dose.

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Maintenance: Sublingual or buccal: Target dose: Buprenorphine 16 mg/naloxone 4 mg once daily; dosage should be adjusted in increments/decrements of buprenorphine 2 mg/naloxone 0.5 mg or buprenorphine 4 mg/naloxone 1 mg to a level that maintains treatment and suppresses opioid withdrawal symptoms; usual range: Buprenorphine 4 to 24 mg/naloxone 1 to 6 mg once daily. Buprenorphine doses ≥16 mg/day have been associated with greater efficacy; limited evidence exists for doses >24 mg/day.

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1. Permanently allows clinicians to prescribe buprenorphine via a phone visit or audiovisual visit.

2. Allows nonphysician practitioners in opioid treatment programs to prescribe methadone.

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3. Allows patients to receive take-home doses of methadone and the initiation of methadone treatment via telehealth and buprenorphine via telehealth

4. Nurse practitioners and physician assistants can order medications in OTPs where state law allows.

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5. Removes requirement that patients receive an opioid use disorder diagnosis at least 12 months before allowed to begin an inpatient treatment program. People can get access to programs mor quickly. .

6. Allows patients to take home up to 7 days of methadone doses during first 14 days of treatment; up to 14 doses if in treatment for at least 15 days, and up to 28 doses if in treatment for 31 days.

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Generic Name	For the Treatment of	Effects	Potential Side Effects	Advantages	Disadvantages
Buprenorphine Buprenorphine (with or without naloxone)	Opioid withdrawal management; Ongoing treatment of opioid use disorder	Improved retention in treatment at doses of 16 mg or higher, reduced withdrawal symptoms and cravings, reduced illicit opioid use, reduced mortality	Constipation, nausea, precipitated withdrawal, excessive sweating, insomnia, peripheral edema, respiratory depression when with benzodiazepines or other CNS depressants, misuse potential, NOWS Implant: Nerve damage during insertion/ removal, accidental overdose or misuse if extruded, local migration or protrusion Subcutaneous: Injection site itching or pain, death from intravenous injection	Ceiling effects on respiratory depression, more rapid induction to steady state dose, less potential for euphoria (compared to methadone), considered safe for office-based treatment; improved social functioning; associated with reductions in criminal activity and recidivism; and infectious disease acquisition and transmission	Requires X-Waiver to prescribe; risk for overdose when combined with alcohol, benzodiazepines, or other sedatives

Generic Name	For the Treatment of	Effects	Potential Side Effects	Advantages	Disadvantages
Naltrexone Naltrexone	Prevention of relapse to opioid use disorder following complete opioid withdrawal	Reduced illicit opioid use, reduced cravings	Nausea, anxiety, insomnia, precipitated withdrawal, hepatotoxicity, vulnerability to opioid overdose, depression, suicidality, muscle cramps, dizziness or syncope, somnolence or sedation, anorexia, decreased appetite or other appetite disorders Intramuscular: Pain, swelling, induration (including some cases requiring surgical intervention)	No risk for misuse or physiological dependence; no special regulatory requirements; improved social functioning; associated with reductions in criminal activity and recidivism; and infectious disease acquisition and transmission	Patients must be fully withdrawn from opioids before beginning treatment, lower retention in treatment, high rates of medication nonadherence, has not been demonstrated to reduce mortality (and may increase mortality risk after medication discontinuation)

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Dental Concerns – Methadone

- 1. Methadone is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsades de pointes. The risk of drug-induced torsades de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution.

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Dental Concerns – Methadone

- 2 Hypotension: May cause hypotension (including orthostatic hypotension and syncope); Monitor for symptoms of hypotension especially following dose initiation or dose titration.

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Dental Concerns – Methadone

- 3. Benzodiazepines or other CNS depressants: Concomitant use of opioids with benzodiazepines or other CNS depressants is a risk factor for respiratory depression and death. Avoid using any benzodiazepine or nitrous oxide in your treatment plan

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Dental Concerns – Methadone

4. Avoid opioid-type pain relivers including hydrocodone, oxycodone, codeine and tramadol for post-surgical pain control. NSAIDs such as ibuprofen OK

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Dental Concerns – Buprenorphine

- 1. The US Food and Drug Administration (FDA) is warning that dental problems have been reported with medicines containing buprenorphine that are dissolved in the mouth (buccal film, sublingual tablets). The dental problems, including tooth decay, cavities, oral infections, and loss of teeth, can be serious and have been reported even in patients with no history of dental issues. Dentists treating someone taking a transmucosal buprenorphine product should perform a baseline dental evaluation and caries risk assessment, establish a dental caries preventive plan, and encourage regular dental checkups.

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- 2. A search of the FDA Adverse Event Reporting System (FAERS) database and the medical literature (Ahmed 2021, Suzuki 2013) through 2018, identified 305 cases of dental adverse events reported with transmucosal buprenorphine use. Patients with opioid use disorder may have a higher incidence of poor dental health (Yazdanian 2020); however, 10% of patients reported no prior history of dental problems. The majority of patients were using transmucosal buprenorphine products.

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Many cases reported a combination of dental decay, tooth loss, and tooth fractures in numerous teeth. Of the 305 cases, 151 were treated for the adverse event, with 47% (71/151) requiring tooth extraction. Other treatments included root canal, dental surgery, and other restorative procedures such as crowns and implants.

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- 3. The case series by Suzuki 2013, described patients with opioid dependence who reported worsening dental problems after the initiation of buprenorphine. This case series included 11 patients, who were taking sublingual buprenorphine for a mean of 45.7 months at a mean dose of 11.6 mg daily.

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- Educate patients to rinse mouth thoroughly after the dose has completely dissolved. Have patients schedule regular dental check ups and have any dental pain assessed as soon as possible. Delay brushing for an hour after dose has dissolved.

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4. Avoid opioid-type pain relivers including hydrocodone, oxycodone, codeine and tramadol for post-surgical pain control. NSAIDs such as ibuprofen OK

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- 5. Benzodiazepines or other CNS depressants: Concomitant use of opioids with benzodiazepines or other CNS depressants is a risk factor for respiratory depression and death. Avoid using any benzodiazepine or nitrous oxide in your treatment plan

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Summary: Drugs Used to Treat Dependence and Addiction

Subclass	Mechanism of Action	Effects	Clinical Application	Pharmacokinetics, Toxicities, Interactions
OPIOID RECEPTOR ANTAGONIST				
• Naloxone	Nonselective antagonist of opioid receptors	Reverses the acute effects of opioids; can precipitate severe abstinence syndrome	Opioid overdose	Effect much shorter than morphine (1-2 h), therefore several injections required
• Naltrexone	Antagonist of opioid receptors	Blocks effects of illicit opioids	Treatment of alcoholism	Half-life ~ 4 h
SYNTHETIC OPIOID				
• Methadone	Slow-acting agonist of μ-opioid receptor	Acute effects similar to morphine (see text)	Substitution therapy for opioid addicts	High oral bioavailability • half-life highly variable among individuals (range 4-130 h) • *Toxicity:* Respiratory depression, constipation, miosis, tolerance, dependence, and withdrawal symptoms
PARTIAL μ-OPIOID RECEPTOR AGONIST				
• Buprenorphine	Partial agonist at μ-opioid receptors	Attenuates acute effects of morphine	Oral substitution therapy for opioid-addicts	Long half-life (40 h) • formulated together with naloxone to avoid illicit IV injections

Supplemental Slide