Medication-Assisted Treatment (MAT) in the Emergency Department

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Disclosures

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Pharmacist & Nurse Objectives

- Identify medication-assisted treatment options for opioid use disorder and alcohol use disorder
- Construct an appropriate pharmacotherapy regimen for opioid use disorder and alcohol use disorder
- Counsel a patient on his/her medication-assisted treatment for opioid use disorder and alcohol use disorder

Pharmacy Technician Objectives

- Identify opportunities for administration, storage and dispensing of medications used for opioid use disorder and alcohol use disorder
- List adverse events and safety considerations of medications used for opioid use disorder and alcohol use disorder

Abbreviations

ASAM: American Society of Addiction Medicine
APP: Advanced Practice Provider
AUC: Area under the curve
AUD: Alcohol Use Disorder
CDC: Centers for Disease Control
CI: Confidence Interval
CIWA-Ar: Clinical Institute Withdrawal Assessment of Alcohol Scale, revised
CNS: Central Nervous System
COWS: Clinical Opiate Withdrawal Scale
CrCl: Creatinine Clearance
DA: Dopamine
DRESS: Drug reaction with eosinophilia and systemic symptoms
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG: Electrocardiogram
ED: Emergency Department
GABA: Gamma Aminobutyric Acid
GI: Gastrointestinal
H: Hours
HIV: Human Immunodeficiency virus
IM: Intramuscular
IV: Intravenous
IVPB: Intravenous, piggyback
LFT: Liver Function Tests
MAT: Medication Assisted Treatment
Min: Minutes
NAc: Nucleus Accumbens
NMDA: N-Methyl-d-aspartic acid
NSAIDs: Non-steroidal Anti-Inflammatory
OUD: Opioid Use Disorder
PO: Oral
SAMHSA: Substance Abuse and Mental Health Services
SBP: Systolic Blood Pressure
SD: Standard Deviation
SubQ: Subcutaneous
TIP: Treatment Improvement Protocol
VTA: Ventral Tegmental Area
XR: Extended Release

Part I. Opioid Use Disorder (OUD)

DSM-5 defines OUD as a problematic pattern of opioid use leading to clinically significant impairment or distress

To confirm a diagnosis, **at least two** of the following should be observed **within 12 months**:

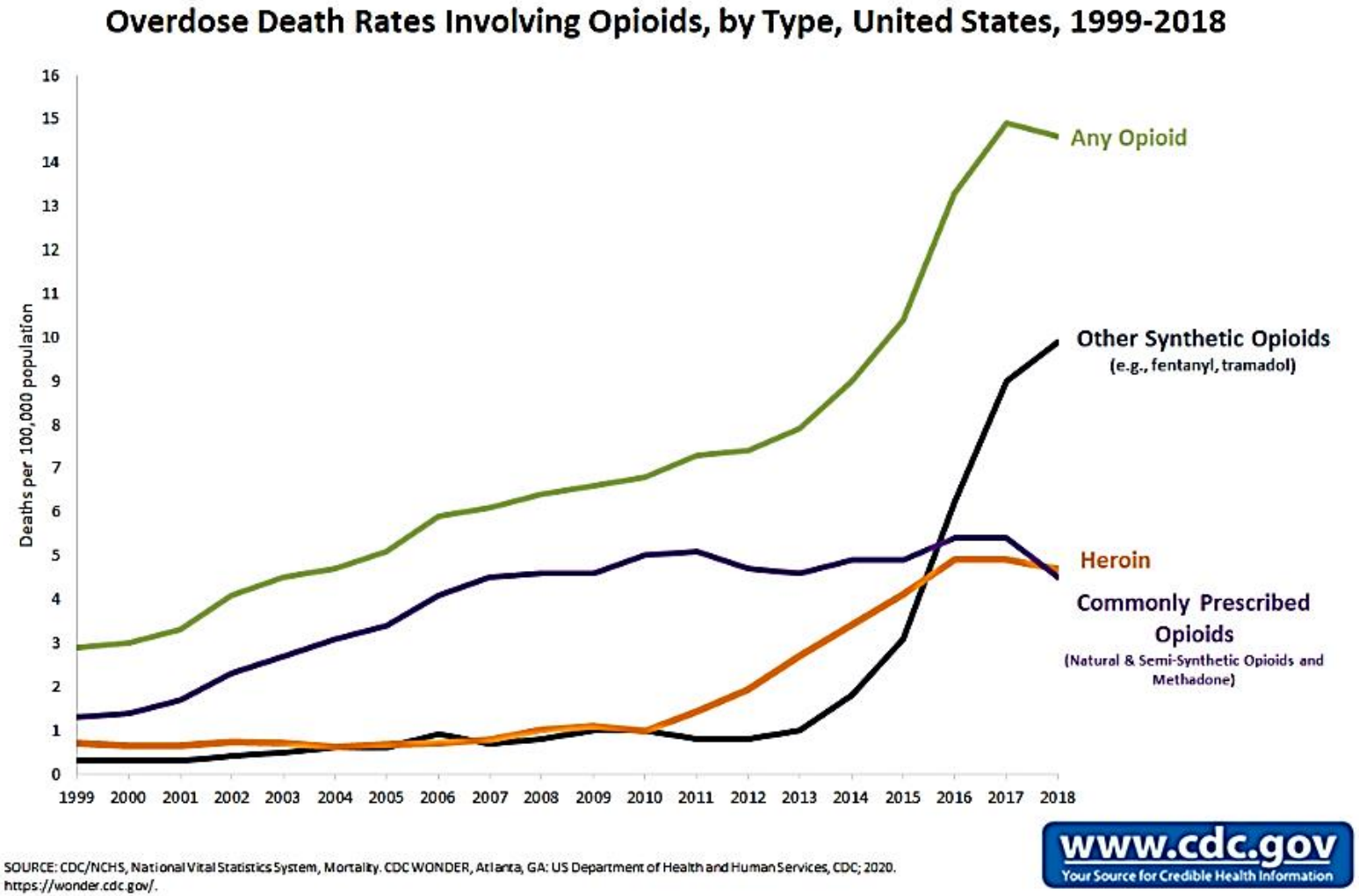
- Craving or strong desire or urge to use
- Interference with obligations
- Opioids used in physically hazardous situations
- Taken in larger quantity or longer duration than intended
- Continuing desire to cut back but failure to do so
- Significant time spent obtaining/using opioid or recovering from effects
- Continued use despite social/interpersonal problems
- Important activities abandoned or reduced due to opioid use
- Tolerance
- Withdrawal

Scoring

2-3	Mild
4-5	Moderate
6+	Severe

Source: American Psychiatric Association. DSM-V

More than 450,000 people have died since 1999 from a drug overdose



"Opioids were involved in nearly **47,000** deaths in 2018, which is nearly **six times** the number of opioid-involved overdose deaths in 1999."

Sources:
https://www.cdc.gov/drugoverdose/data/statedeaths.html, retrieved 05/15/2020
https://www.cdc.gov/drugoverdose/data/analysis.html, retrieved 05/15/2020

Opioid overdose deaths can be outlined in three distinct waves

1990

- Increase in prescription opioids (natural and semi-synthetic opioids)
- Increasing since at least 1999

2010

- Rapid increases in overdose deaths involving heroin

2013

- Synthetic opioids, such as fentanyl

Natural
Opium
Morphine
Codeine
Semi – Synthetic
Oxy-/hydrocodone
Oxy-/hydromorphone
Buprenorphine
Synthetic
Fentanyl
Tramadol
Methadone

Sources:
https://www.cdc.gov/drugoverdose/data/statedeaths.html, retrieved 05/15/2020
https://www.cdc.gov/drugoverdose/data/analysis.html, retrieved 05/15/2020

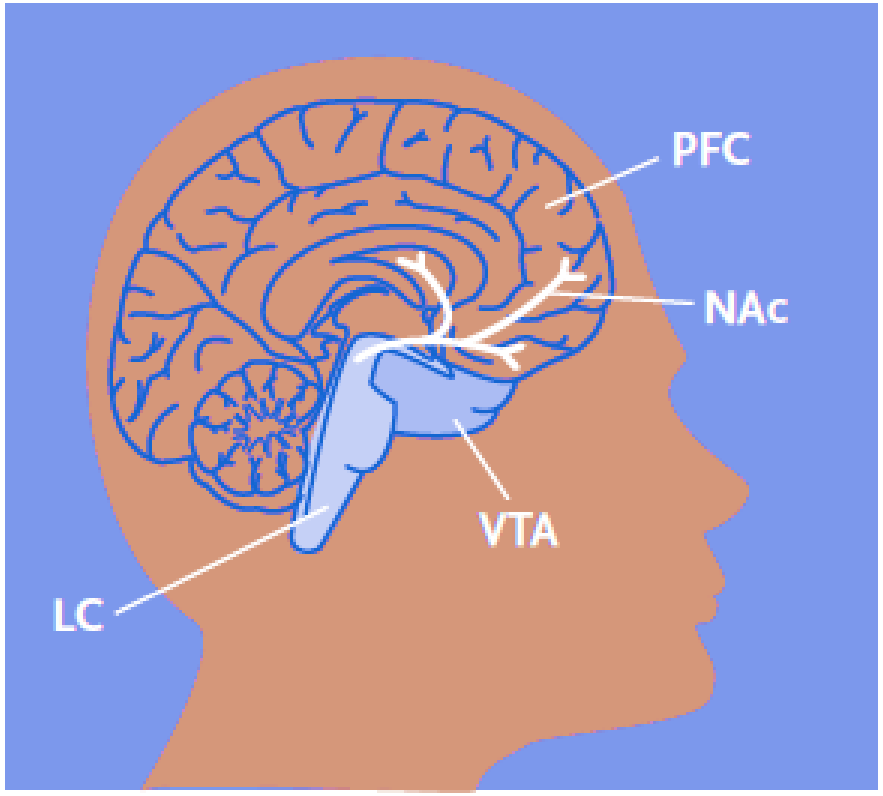
The mu opioid receptor is essential for stimulating the reward system

	Mu	Kappa	Delta
CNS location	Cerebral cortex, thalamus, periaqueductal gray, and rostral ventromedial	Hypothalamus, and periaqueductal gray	Basal ganglia (pontine nucleus, amygdala)
Effects	Analgesia, euphoria, constipation, respiratory depression, physical dependence **Reward reinforcements**	Analgesia, diuresis, dysphoria **Anti-reward**	Analgesia, anxiolysis

- The mu opioid receptor is a main target for MAT therapy

Source: Wang S. *Cell Transplant*. 2019.

Opioids activate the mesolimbic reward system



Stimulation of mu opioid receptors in the brain

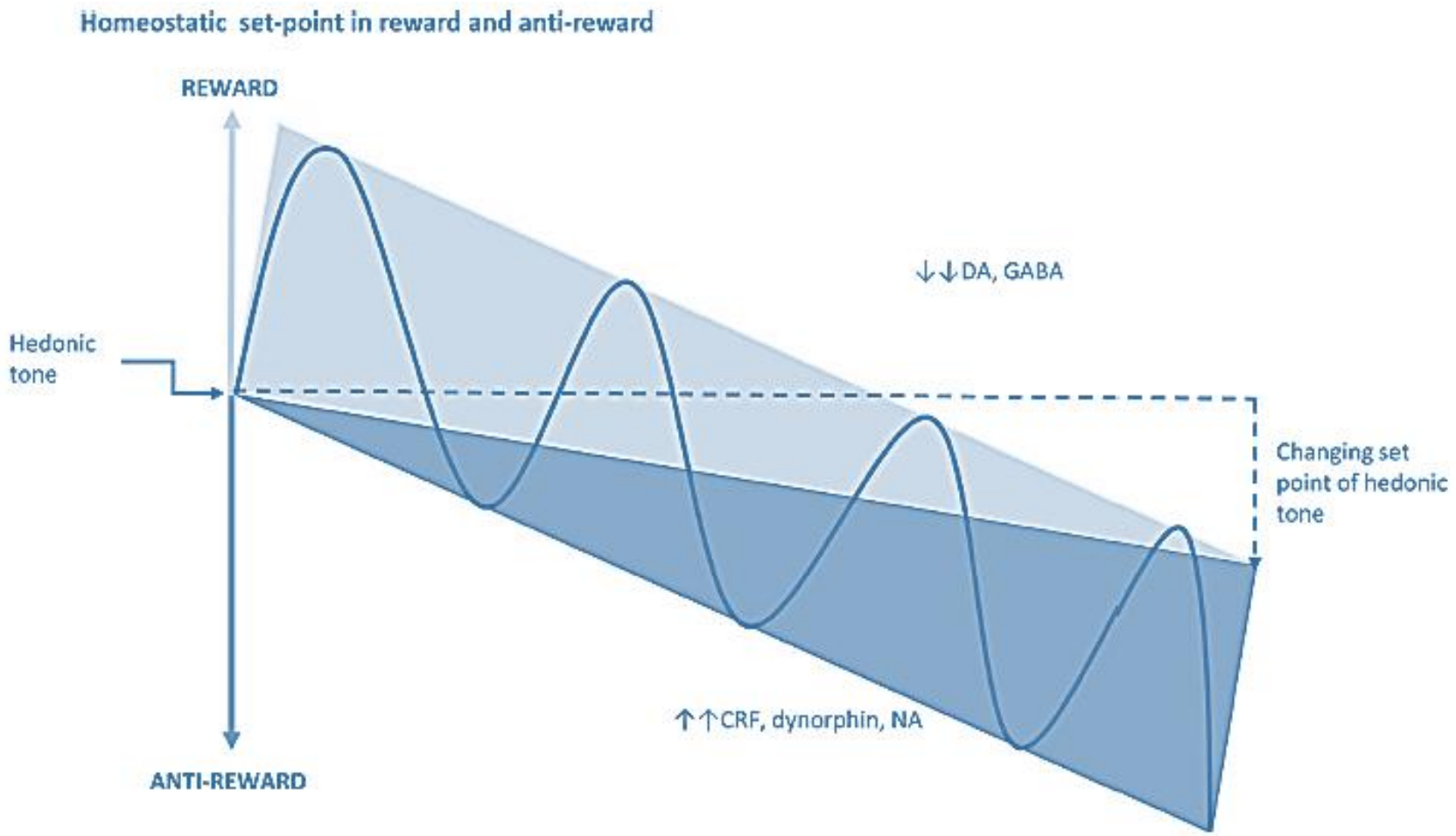
Cells in the ventral tegmental area (VTA) produce dopamine

Dopamine is released into the nucleus accumbens (NAc)

Rise to feelings of pleasure

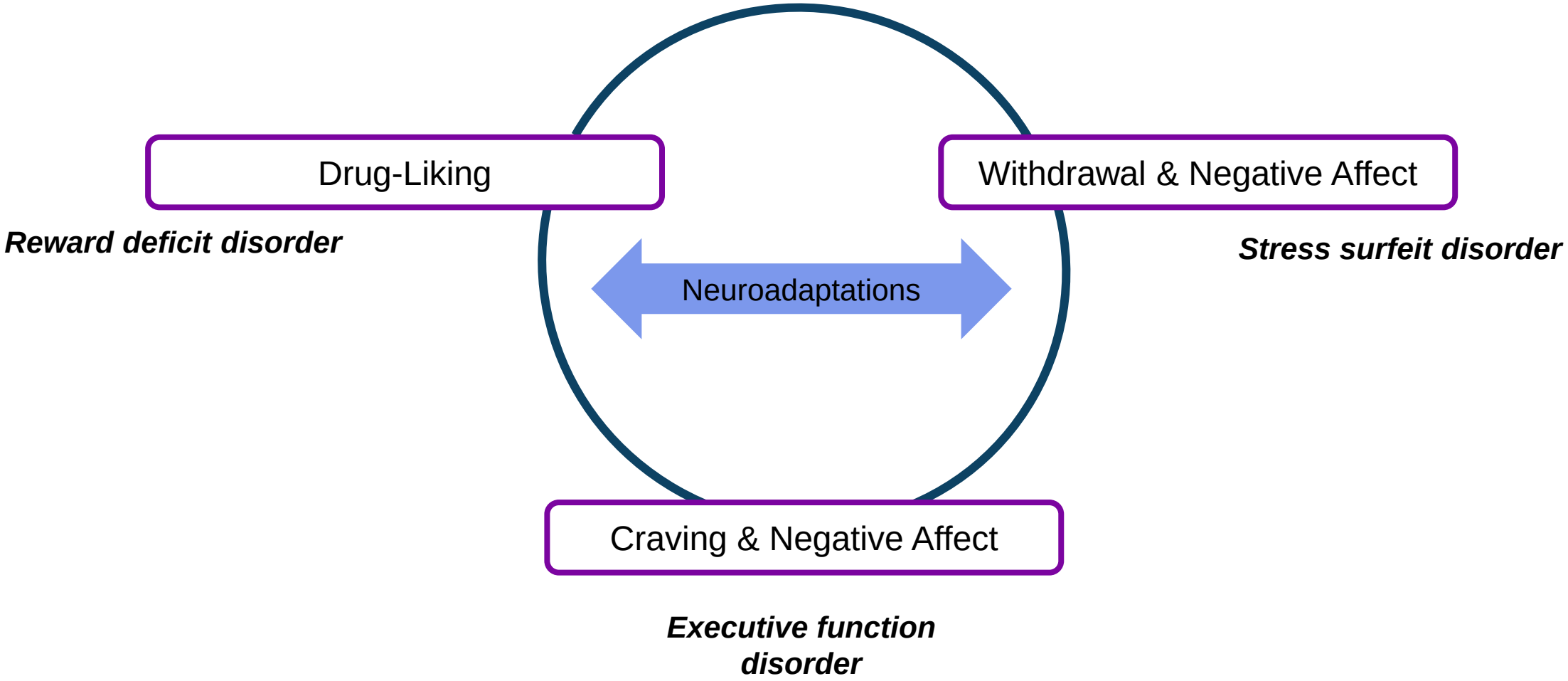
Source: Kosten TR. *Sci Pract Perspect*. 2002.

The set-point of hedonic tone is determined by the balance between the opposing reward and anti-reward pathways



Source: Koob G. *Dialogues Clin Neurosci. 2017.*

There are three key drivers in the cycle of opioid use disorder



Source: Koob G. *Dialogues Clin Neurosci. 2017.*

Part II. MAT for OUD

MAT:
Opioid Use Disorder

Medication-Assisted Treatment (MAT) promotes a “whole patient” approach to the treatment of substance use disorders

Medication + **Behavioral Therapy**

- Clinically effective
- Comprehensive, individually tailored program of medication and behavioral therapy
- Support services that address the needs of most patients

Source: https://www.samhsa.gov/medication-assisted-treatment/treatment#medications-used-in-mat, retrieved 05/10/2020.

The ultimate goal of MAT is full recovery

MAT has been shown to

- Improve patient survival
- Decrease illicit opiate use and other criminal activity among people with substance use disorders
- Increase patients' ability to gain and maintain employment
- Improve birth outcomes among women who have substance use disorders and are pregnant
- Decreases opioid use, opioid-related overdose deaths, infectious disease transmission
- Increases social functioning and retention in treatment

Sources:
https://www.samhsa.gov/medication-assisted-treatment/treatment#medications-used-in-mat, retrieved 05/10/2020.
https://www.drugabuse.gov/publications/effective-treatments-opioid-addiction/effective-treatments-opioid-addiction, retrieved 05/11/2020.

A common misconception is that MAT substitutes one drug for another

- Rather, the medications relieve the withdrawal symptoms and psychological cravings that cause chemical imbalances in the body
- MAT programs provide a safe and controlled level of medication
- MAT medications can safely be taken for months, years or even a lifetime

Source: https://www.samhsa.gov/medication-assisted-treatment/treatment#medications-used-in-mat, retrieved 05/10/2020.

The importance of starting medication is conveyed through recent language in ASAM's guidelines

"Patients' psychosocial needs should be assessed, and patients should be offered or referred to psychosocial treatment based on their individual needs.

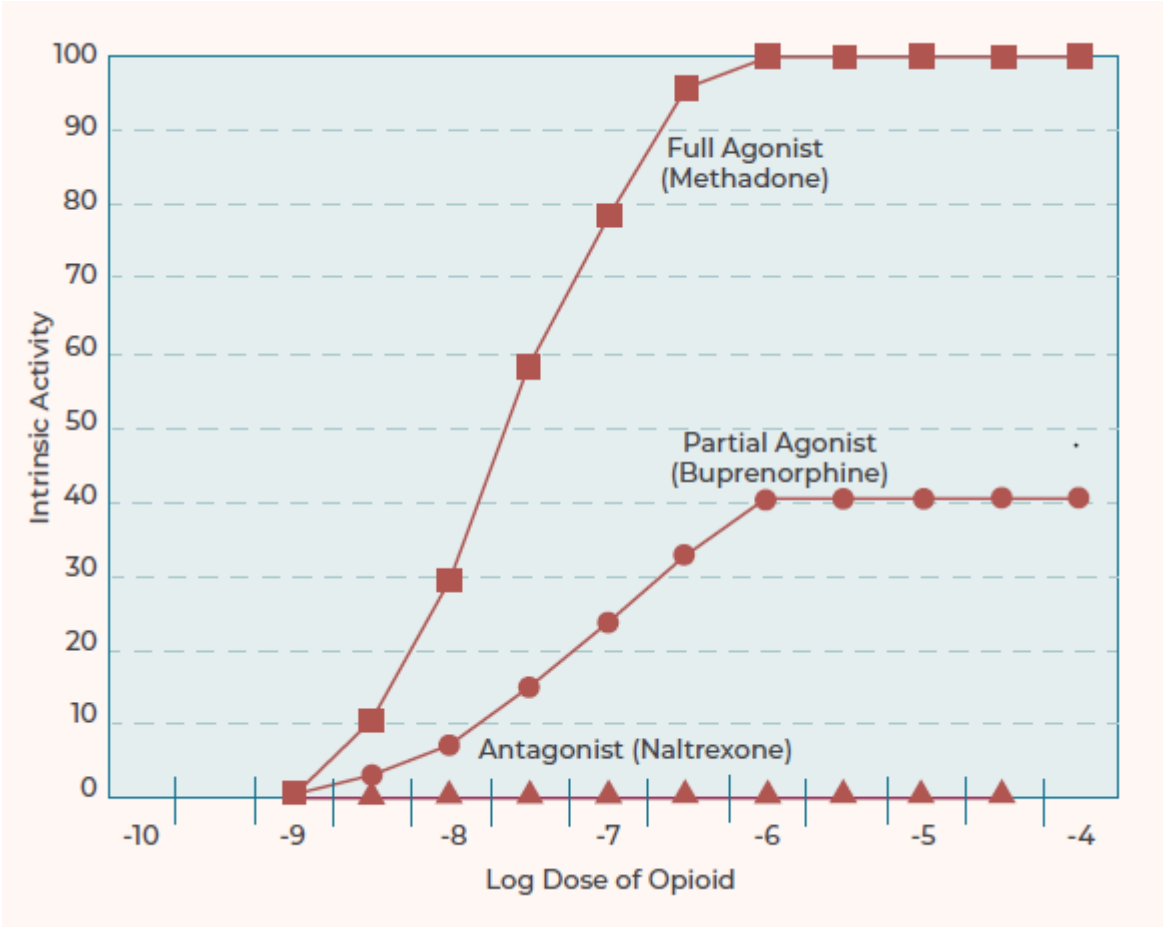
However, a patient's decision to decline psychosocial treatment or the absence of available psychosocial treatment should not preclude or delay pharmacotherapy, with appropriate medication management.

Motivational interviewing or enhancement can be used to encourage patients to engage in psychosocial treatment services appropriate for addressing individual needs."

American Society of Addiction Medicine (ASAM), 2020 Update

Source: Crotty K. *J Addict Med*. 2020.

The amount of intrinsic activity corresponds to the amount of opioid receptor agonist effects



Source: SAMHSA. Opioid Use Disorder: Treatment Improvement Protocol. 2020.

Methadone

Mechanism of action
- Long-acting, full mu-opioid agonist

Dosing
- Initiate dosing regimen for each patient individually
- Maximum initial dose 30 mg PO
- Observe patients for over-sedation and withdrawal symptoms for 2 to 4 hours after initial dose
- Do not increase dose without waiting for steady-state (3 to 5 days) to be achieved
- Usual maintenance range 80-120 mg/day

Administration and storage
- Store at room temperature

Onset	0.5-1 h
Peak	3-5 days
Duration	22-48 h

Monitoring
- Cardiac: ECG to monitor QT interval and hypotension
- Respiratory depression
- Constipation

Counseling
- Avoid taking this with alcohol, may cause drowsiness

Sources:
Methadone. In: Lexi-Drugs, retrieved 05/10/2020.
Toce MS. *J Med Toxicol*. 2018.

Naltrexone

Mechanism of action: pure opioid antagonist, with highest affinity for mu receptors

Dosing

- PO 25 mg initially, then 50 mg/day thereafter if no withdrawal symptoms
- IM 380 mg once every 4 weeks

Administration and storage

- Tablet: store at room temperature
- Injection: store unopened kit in the refrigerator; kit can be kept at room temperature for ≤7 days prior to use
  - Do not freeze
  - Following reconstitution of the suspension, administer immediately
- Do not administer IV, SubQ or into fatty tissue

Peak	PO: 60 min IM: 2 h, 2-3 days
Duration	PO: 24-72 h IM: 4 weeks

Sources:
Naltrexone. In: Lexi-Drugs, retrieved 05/10/2020.
Toce MS. *J Med Toxicol*. 2018.

Naltrexone

Monitoring

- Acute opioid withdrawal
- Injection site reactions
- Suicidal thoughts/depression
- Liver function tests (baseline and periodic)
    - Naltrexone AUC increased 5-10 fold in patients with compensated or decompensated hepatic cirrhosis respectively

Counseling

- Do not attempt to overcome the opioid blocker during therapy, as it could lead to a potential fatal overdose

Considerations

- Do not initiate therapy until patient is opioid-free for at least 7-10 days after last opioid use; up to 14 days may be necessary for patients on long-acting opioids

Sources:
Naltrexone. In: Lexi-Drugs, retrieved 05/10/2020.
Toce MS. *J Med Toxicol*. 2018.

Buprenorphine

Mechanism of action: partial mu-agonist

- Binds to kappa and delta opioid receptors with lower affinity
- Higher affinity, lower intrinsic activation than many full agonists (heroin, oxycodone, morphine)

Considerations for initiation

- Do not administer buprenorphine until moderate symptoms of opioid withdrawal have developed
- Period of abstinence required will vary due to half-life of opioid
  - ≥ 6 to 12 hours after last use of short-acting opioids (i.e., heroin, oxycodone)
  - 24 to 72 hours after last use of long-acting opioids (i.e., methadone)

Formulations of buprenorphine

Buprenorphine sublingual tablets (Subutex®)
Buprenorphine/naloxone sublingual films (Suboxone®)
Buprenorphine/naloxone sublingual tablets (Zubsolv®)
Buprenorphine/naloxone buccal film (Bunavail®)
Buprenorphine implants (Probuphine®)
Buprenorphine extended-release injection (Sublocade®)

Onset	IM: 15 min
Peak	Buccal film: 2.5-3 h XR SubQ: 24 h Sublingual: 30 min-1 h Transdermal patch: 3 days

Sources:
Buprenorphine. In: Lexi-Drugs, retrieved 05/10/2020.
Toce MS. *J Med Toxicol*. 2018.

Buprenorphine

Preparation	Dosing	Administration and storage
Sublingual tablet	• Initial 2-4 mg sublingual • If no signs of precipitated withdrawal after 60-90 minutes, may increase in increments of 2-4 mg • Consider an initial dose of 1 mg in patients with a history of opioid use disorder with a high risk of relapse but not currently dependent on opioids. Titration in these patients should occur more slowly	• Place tablet under the tongue until dissolved (can take up to 10 minutes) • Do not chew or swallow • To ensure consistent bioavailability, take subsequent doses the same way • Store at room temperature
Extended-release injection	• Initial SubQ 300 mg monthly for the first 2 months • Maintenance 100 mg monthly	• Administer doses $\geq$ 26 days apart • Store in refrigerator, bring to room temperature before administration • Room temperature – discard after 7 days
Subdermal implant	• 4 implants inserted into the inner side of the upper arm 12-24 hours after last dose of transmucosal buprenorphine product	• Remove within 6 months • Can insert 4 new implants into other arm • Store at room temperature

Source: Buprenorphine. In: Lexi-Drugs, retrieved 05/10/2020.

Buprenorphine

Preparations

- Frequently co-formulated with naloxone to deter IV abuse
  - Mu-opioid receptor antagonist
  - Naloxone has negligible oral bioavailability

Contraindications

- Significant respiratory depression; acute or severe asthma in an unmonitored setting or in the absence of resuscitative equipment; GI obstruction, including paralytic ileus (known or suspected).

Monitoring

- CNS and respiratory depression
- Hepatoxicity: monitor LFT in patients at increased risk for hepatoxicity
- Hypotension
- QT prolongation: Do not exceed a dose of 900 mcg every 12 hours buccal film or one 20 mcg/hour transdermal patch

Sources:
Buprenorphine. In: Lexi-Drugs, retrieved 05/10/2020.
Toce MS. *J Med Toxicol*. 2018.

Initiation of buprenorphine for patients with opioid use disorder in the ED is efficacious and safe

D'Onofrio et al. JAMA. 2015;313(16):1636-1644.	
Design **Setting** **Population**	Randomized clinical trial N=329 opioid dependent patients at an urban teaching hospital ED April 2009-June 2013
Intervention	1. Screening and referral to treatment 2. Screening, brief intervention, and facilitated referral to community-based treatment services 3. Screening, brief intervention, ED-initiated treatment with buprenorphine/naloxone, and referral to primary care for 10-week follow-up
Outcomes	Primary: • Enrollment in and receiving addiction treatment 30 days after randomization Secondary: • Self-reported days of illicit opioid use • Urine testing for illicit opioids • HIV risk • Use of addiction treatment services

Source: D'Onofrio G. *JAMA*. 2015.

Initiation of buprenorphine for patients with opioid use disorder in the ED is efficacious and safe

Results	Primary outcome (engaged in addiction treatment 30 days after randomization), **p<0.001** • 89/114 (**78%** [95% CI, 70-85%]) in buprenorphine group vs. • 38/102 (**37%** [95% CI, 28-47%]) in the referral group vs. • 50/111 (**45%** [95% CI, 36-54%]) in the brief intervention group Secondary outcomes • Rates of urine samples that tested negative for opioids did not differ statistically across groups (p=0.17) • No statistically significant differences in HIV risk across groups (p=0.66) • 11% of patients in the buprenorphine group (95% CI, 6-19%) used inpatient addiction treatment services, compared to 37% in the referral group (95% CI, 27-48%) and 35% in the brief intervention group (95% CI, 25-37%) (**p<0.001**)
Conclusion	Among opioid-dependent patients, ED-initiated buprenorphine treatment vs brief intervention and referral significantly increased engagement in addiction treatment, reduced self-reported illicit opioid use, and decreased use of inpatient addiction treatment services but did not significantly decrease the rates of urine samples that tested positive for opioids or of HIV risk.

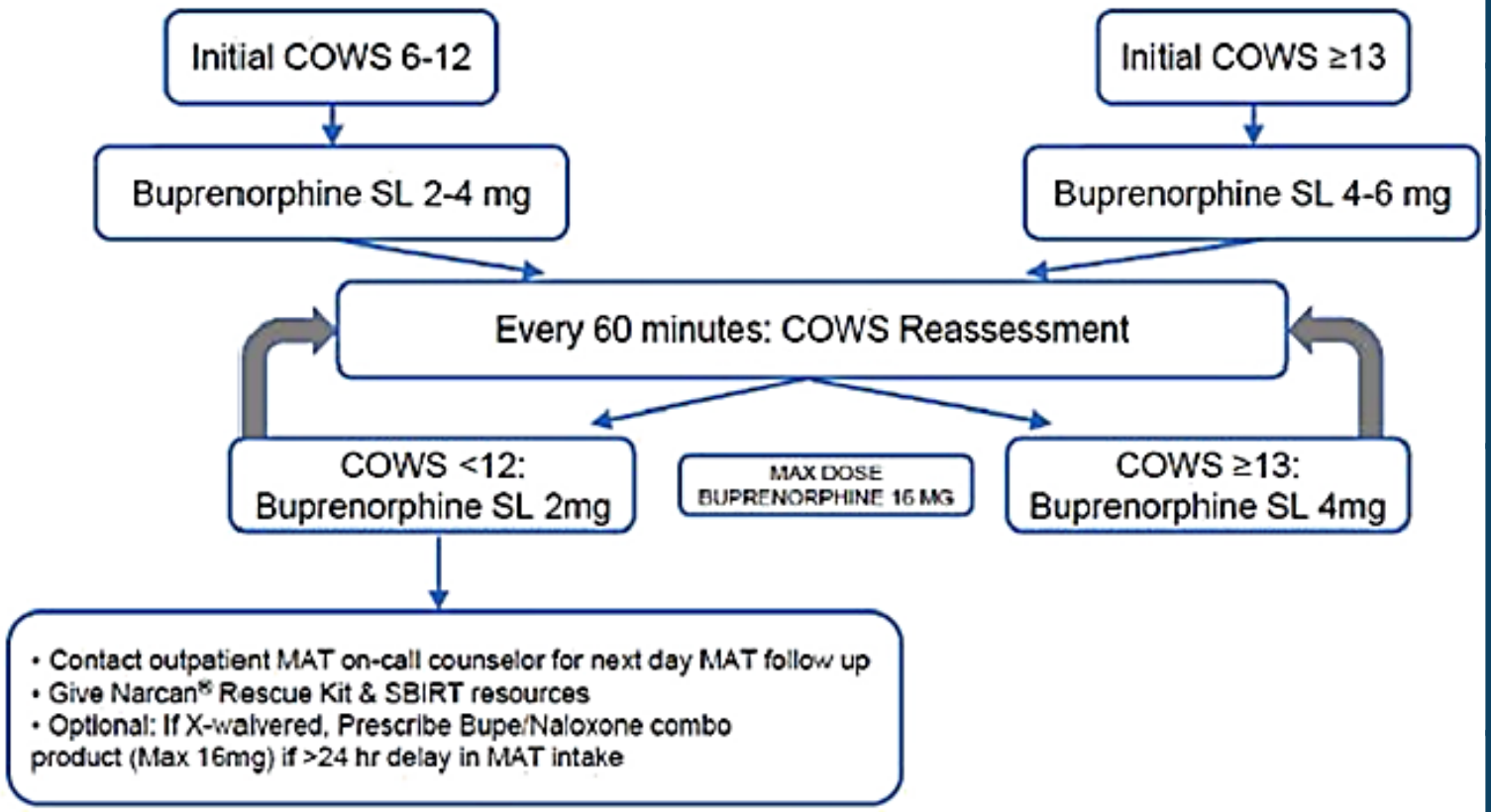
Source: D'Onofrio G. *JAMA*. 2015.

ED-based buprenorphine induction program

Kaucher KA et al. Am J Em Med. 2020;38:300-304.	
Design **Setting** **Population**	Single center, retrospective analysis at Denver Health Medical Center (academic public safety-net institution, with 525 inpatient beds and 9 community health centers) May 2017 and October 2018 Potential candidates if they have expressed interest or if the provider offered services and they accepted N=219
Outcomes	<u>Primary:</u> Follow-up or intake at institution's own outpatient MAT facility after ED induction Retention rates at 30 days after induction <u>Secondary:</u> Buprenorphine dosing for induction ED length of stay Patient demographics

Source: Kaucher KA. *Am J Em Med*. 2020.

Buprenorphine induction process doses were based on SAMHSA's Treatment Improvement Protocol 40



	No. (%)
Total number of patients	219
Male	123 (56.2)
Age, mean (SD), y	35 (10.3)
Race White Black Other	 189 (86) 14 (6) 16 (8)
Most commonly abused opioid IV Opioid Oxycodone Hydrocodone Other	 165 (75) 23 (10.5) 4 (1.8) 27 (12.3)
Advanced Practice Provider (APP) Attending/Resident Physician	127 (58) 92 (42)

COWS: Clinical Opiate Withdrawal Scale to assess withdrawal severity

APP's were a group of practitioners trained to manage buprenorphine induction patients in the ED

Source: Kaucher KA. *Am J Em Med*. 2020.

ED-based buprenorphine induction program

	No. (%) of Patients
Primary outcome	
Enrolled in MAT at 30 days	108 (49.3)
Secondary outcomes	
Total discharged from MAT Lack of attendance Relocated/incarceration Lack of transportation or clinic hours	111 (50.7) 22 (20) 15 (14) 7 (6)
Arrived at MAT intake within 72 h of induction	162 (74)
Initial COWS score, mean (SD)	13.1 (5.8)
Last COWS score, mean (SD)	3.6 (2.6)
Buprenorphine induction dose, mean (SD)	7.7 (3.3)
MAT Buprenorphine dose, mean (SD)	12.3 (5.6)
Transitioned to MAT methadone	31 (14)

Challenges and considerations

- Education on the Code of Federal Regulations, Part 1306.07 “3-day rule” was needed to make providers comfortable with providing buprenorphine
- Initial dosing of 2-4 mg to those in moderate withdrawal was likely inadequate, requiring several additional doses and reassessments
  - Potential under-treatment effect

Source: Kaucher KA. *Am J Em Med*. 2020.

Summary of comparison of MAT therapy

	Methadone	Naltrexone	Buprenorphine
Mechanism of action	Full mu agonist NMDA antagonist	Full mu antagonist	Partial mu agonist Kappa antagonist Delta antagonist
Clinical pearls	Risk of over/sedation and respiratory depression “Start low, go slow”	Must be opioid-free for 7 to 10 days to reduce risk of precipitated withdrawal	Low risk of overdose and respiratory depression “Ceiling effect”
Appropriate patients	Typically for patients with OUD who are physiologically dependent on opioids.	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.	Typically for patients with OUD who are physiologically dependent on opioids.

Source: SAMHSA. Opioid Use Disorder: Treatment Improvement Protocol. 2020.

Methadone or buprenorphine can be used as MAT therapy in pregnant patients

Pregnancy

- Women who are physically dependent on opioids should receive treatment using methadone or buprenorphine over withdrawal management/abstinence
- Treatment with methadone should be initiated as early as possible during pregnancy
- PK of methadone is affected by pregnancy
  - Advancing gestational age → plasma levels of methadone progressively decrease → clearance increases
  - Increased or split doses may be needed as pregnancy progresses
  - Dose may need to be adjusted after birth
- Buprenorphine is a reasonable and recommended alternative to methadone

Source: SAMHSA. Opioid Use Disorder: Treatment Improvement Protocol. 2020.

Further research is needed to examine the efficacy of pharmacotherapy for adolescents with opioid use disorder

Adolescents

- Opioid agonists (methadone or buprenorphine) and antagonists (naltrexone) may be considered
- Efficacy studies were largely conducted in adults
- Agonist medications are indicated for age 18 and older
  - Exception for age 16 and 17: documented history of at least two prior unsuccessful withdrawal management attempts, and have parental consent
- Buprenorphine has been studied in adolescents over 16 years
- Naltrexone can be considered for ages over 18
  - Does not induce physical dependence
  - May be particularly useful for adolescents who report a shorter duration of opioid use

Source: SAMHSA. Opioid Use Disorder: Treatment Improvement Protocol. 2020.

Part III. Opioid Withdrawal

Opioid withdrawal can occur after stopping or dramatically reducing the dose of opioid drugs after heavy and prolonged use

- Rarely life-threatening
- Abrupt discontinuation is not recommended as it may precipitate withdrawal, lead to strong cravings and result in relapse

Symptoms	Short-acting	Long-acting
Examples	Heroin, oxycodone	Methadone
Emerge	12 h since last exposure	30 h since last exposure
Peak	24-48 h	3-5 days
Diminish	3-5 days	10 days

- Muscle aches, increased tearing, runny nose, dilated pupils, piloerection, agitation, anxiety, insomnia, sweating, yawning, abdominal cramping, nausea, vomiting, diarrhea

Source: ASAM. National Practice Guidelines. 2015.

Clinical Opiate Withdrawal Scale (COWS) can be used to determine the severity of opioid withdrawal

- Reproducibly rate common signs and symptoms of opiate withdrawal and monitor these symptoms over time
- 11-item scale to be administered by a clinician

1. Resting pulse rate
2. Sweating
3. Restlessness
4. Pupil size
5. Bone or joint aches
6. Runny nose or tearing
7. GI Upset
8. Tremor
9. Yawning
10. Anxiety or irritability
11. Gooseflesh skin

Severity Score

5-12	Mild
13-24	Moderate
25-36	Moderately severe
> 36	Severe

Source: Wesson DR. *J Psychoactive Drugs*. 2003.

Symptom-based therapies

Withdrawal Symptom	Therapy Options
Anxiety, irritability, diaphoresis	Clonidine, lofexidine, olanzapine
Diarrhea	Loperamide
Nausea	Ondansetron, metoclopramide
Insomnia	Diphenhydramine, trazodone
Pain	Acetaminophen, NSAIDs

Clonidine can be used off-label in a medically supervised setting for opioid withdrawal

Evidence

- Research demonstrated effective use of clonidine in controlling acute opioid withdrawal symptoms and lessening the likelihood of severe withdrawal

Mechanism of action

- Alpha2-adrenergic agonist

Dosing

- Initial
  - 0.1-0.2 mg (patients >90 kg may receive up to 0.3 mg)
  - May repeat every 45 to 60 minutes if needed
  - Up to a total of 4 doses until symptoms resolve
- Maintenance
  - 0.1-0.3 mg every 6 to 8 hours determined by symptom severity, maximum 1.2 mg/day
- May transition to an equivalent dose of a transdermal patch after a stable oral dose is established

Sources:
Clonidine. In: Lexi-Drugs, retrieved 05/11/2020.
Duber HC. *Ann Emerg Med*. 2018.

Clonidine can be used off-label in a medically supervised setting for opioid withdrawal

Monitoring

- Bradycardia, hypotension

Counseling points

- Do not stop taking clonidine abruptly to decrease the risk of rebound hypertension and other withdrawal symptoms (nervousness, agitation, headache, tremor)

Considerations

- May not be as effective as other monotherapies for treatment of severe acute opioid withdrawal
- Often used in conjunction with mu-agonist therapy

Sources:
Clonidine. In: Lexi-Drugs, retrieved 05/11/2020.
Duber HC. *Ann Emerg Med*. 2018.
Toce MS. *J Med Toxicol.* 2018.

Lofexidine (Lucemyra©) is FDA-approved for the management of opioid withdrawal

Evidence

- Several randomized double-blinded studies have found similar effectiveness in controlling signs of and symptom of opioid withdrawal among lofexidine and clonidine

Mechanism of action

- Alpha2-adrenergic agonist

Dosing

- 0.54 mg 4 times daily (every 5-6 hours) during peak withdrawal symptoms
  - Adjust dosing based on tolerability and withdrawal symptoms
- May continue up to 14 days if needed
- Maximum dose: 0.72 mg/dose or 2.88 mg/day
- Discontinuation of therapy
  - Decrease dose gradually over 2 to 4 days
    - Reduce by 0.18 mg per dose every 1 to 2 days

Sources:
Lofexidine. In: Lexi-Drugs, retrieved 05/11/2020.
Toce MS. *J Med Toxicol.* 2018.

Lofexidine (Lucemyra©) is FDA-approved for the management of opioid withdrawal

Monitoring

- Hypotension (less common compared to clonidine), dizziness, dry mouth, QT prolongation

Counseling points

- Can be taken with or without food
- Consult with your provider if you experience signs of a abnormal heartbeat or passing out
- Do not stop taking lofexidine abruptly

Sources:
Lofexidine. In: Lexi-Drugs, retrieved 05/11/2020.
Toce MS. *J Med Toxicol.* 2018.

Olanzapine was recently explored as an option to manage opioid withdrawal symptoms

Mechanism of action: 2nd generation antipsychotic with potent antagonism of 5HT2a, 5HT2c, dopamine, H1 and alpha1-adrenergic receptors

Dosing

- IM 10 mg (2 ml)

Administration and storage

- Reconstitute 10 mg vial with 2.1 ml of sterile water for injection to get a resulting concentration of 5 mg/ml
- Do not administer SubQ
- Inject slowly, deep into muscle
- If dizziness and/or drowsiness are noted, patient should remain until examination indicates postural hypotension and/or bradycardia are not a problem
- Store at room temperature, protect from light, do not freeze

Monitoring

- QT prolongation
- Anticholinergic effects
- Extrapyramidal symptoms
- DRESS multiorgan hypersensitivity reaction

Sources:
Olanzapine. In: Lexi-Drugs, retrieved 05/11/2020.
Toce MS. *J Med Toxicol.* 2018.

Intramuscular olanzapine versus oral clonidine

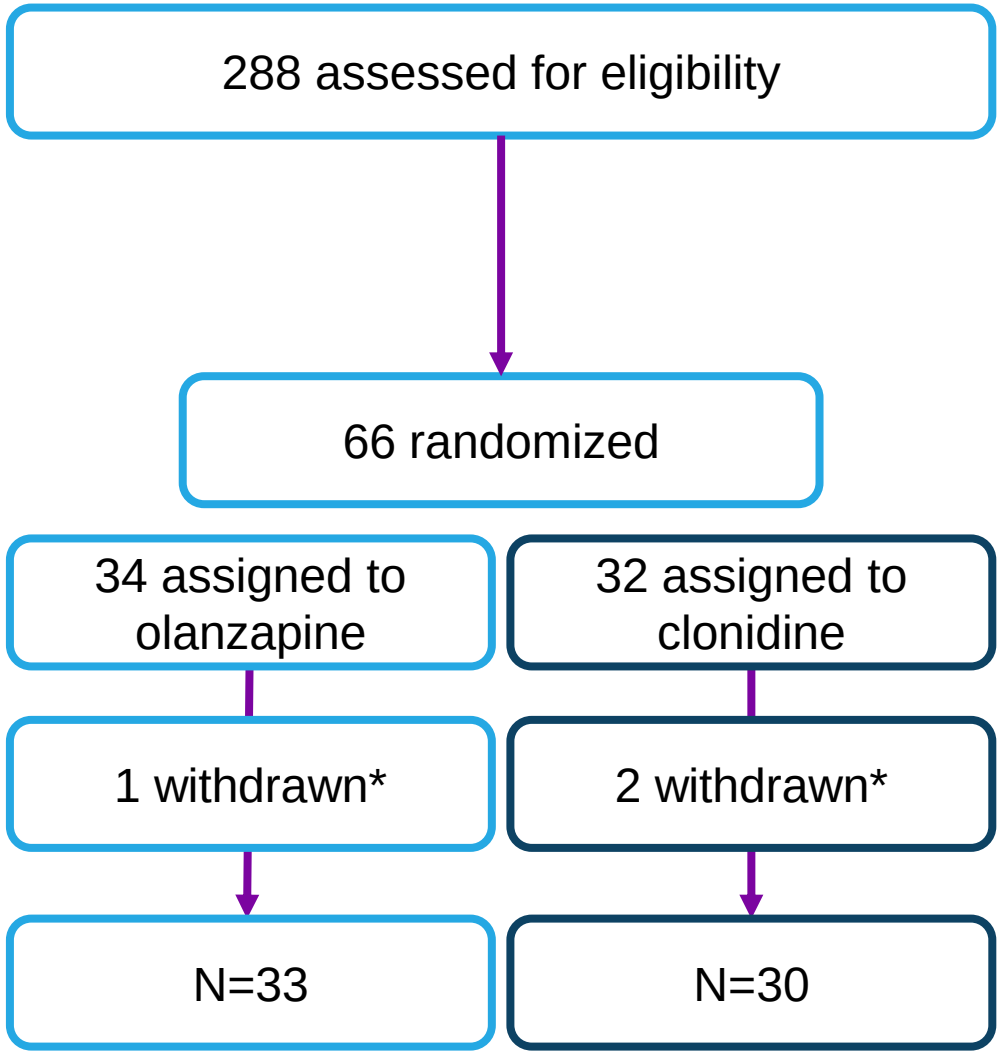
Klein et al. JAMA. 2019;57(8):697-702.	
Design	Randomized, open-label clinical trial October 2015 to June 2017
Intervention	• 10 mg of IM olanzapine • 0.3 mg of oral clonidine After administration, mandatory 30-min interval in which the patient could not receive other additional interventions After the 30-min interval, the provider could give the patient additional rescue medication • Not dictated by study protocol, was at the discretion of the provider • Could receive additional dose of study medication, cross-over, or receive another treatment
Outcomes	Primary: need for rescue medication 60 minutes after study drug administration • Olanzapine, clonidine, ondansetron, metoclopramide, prochlorperazine, diphenhydramine, acetaminophen, ibuprofen, haloperidol, ketamine, benzodiazepines Secondary: • Rescue medication within 2 hours or entire encounter • Change in COWS score • Return visit within 7 days for withdrawal and for any reason

Source: Klein LR. *Clin Toxicol*. 2019.

Intramuscular olanzapine versus oral clonidine

Inclusion
- ≥ 18 years of age
- Provided history of recent opioid use
- Experiencing symptomatic opioid withdrawal
- Required medical treatment for their symptoms per the ED provider's discretion

Exclusion
- Pregnant
- Incarcerated
- Suicidal
- Unable to provide written informed consent in English
- Hypotensive (SBP<90 mmHg)
- Known allergy to either study medication
- Already received treatment for opioid withdrawal during ED encounter
- Patients were not excluded if they took their own medications prior to arrival

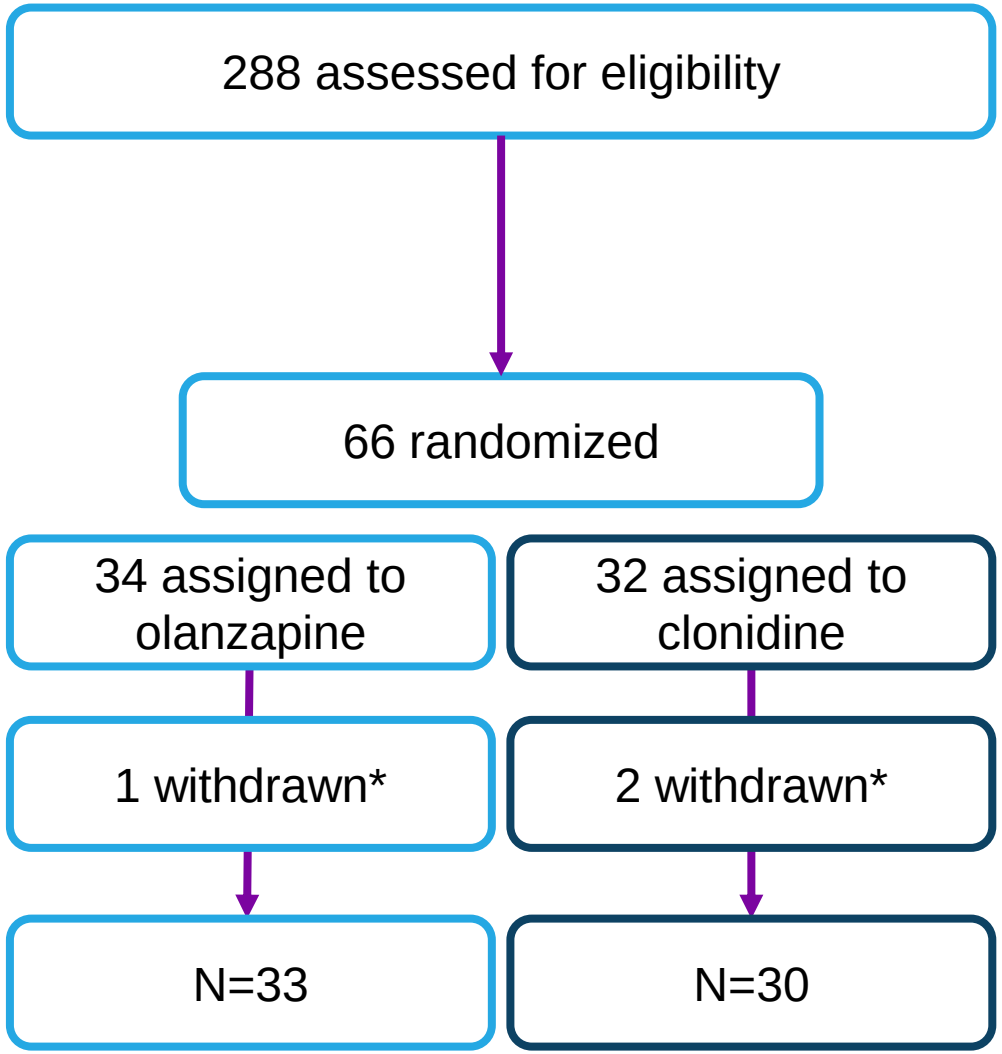


*Patients eloped from hospital prior to receiving medication

Source: Klein LR. *Clin Toxicol*. 2019.

Intramuscular olanzapine versus oral clonidine

	Olanzapine	Clonidine
Age (median, range)	35 (22-60)	34 (21-67)
Gender (male)	21 (63%)	15 (50%)
Home antipsychotic use	6 (18%)	5 (17%)
Baseline COWS (median, range)	11 (4-23)	11 (4-22)
Chronicity of opioid use		
<6 months	4 (12%)	4 (13%)
6 months–1 year	3 (9%)	6 (20%)
1 year–5 years	12 (36%)	10 (33%)
>5 years	14 (42%)	10 (44%)
Comorbidities		
Schizophrenia	0	1 (3%)
Bipolar disorder	5 (15%)	5 (17%)
Anxiety	7 (21%)	3 (10%)
Depression	6 (18%)	8 (27%)
Opiates used within last 7 days		
Heroin	19 (58%)	10 (33%)
Methadone	8 (24%)	9 (30%)
Oxycodone/hydrocodone	5 (18%)	4 (22%)
Oxycontin©	3 (9%)	2 (7%)
Buprenorphine	1 (4%)	1 (6%)



*Patients eloped from hospital prior to receiving medication

Source: Klein LR. *Clin Toxicol*. 2019.

IM Olanzapine versus oral clonidine

	Olanzapine	Clonidine	Difference (95% CI)
Primary outcome			
Rescue medications within 1 h	9 (27%)	19 (63%)	-36% (-59 to -15%)
Clonidine	5 (15%)	1 (3%)	12% (-2 to 25%)
Olanzapine	4 (12%)	7 (23%)	-11% (-30 to 8%)
Ondansetron	4 (12%)	11 (37%)	-25% (-46 to -4%)
Ibuprofen/acetaminophen	2 (6%)	2 (7%)	-1% (-13 to 11%)
Diphenhydramine	1 (3%)	4 (13%)	-10% (-23 to 33%)
Benzodiazepines	2 (6%)	4 (13%)	-7% (-21 to 8%)
Secondary outcomes			
Rescue medication, within 2 hours	12 (36%)	24 (80%)	-44% (-66 to -22%)
Rescue medication, entire encounter	14 (46%)	25 (83%)	-37% (-59 to -15%)
Change in COWS score, 1 hour (mean)	8.3	5.1	3.2 (0.3 to 6.0)
Change in COWS score, final (mean)	9.9	7.8	2.1 (-1 to 5.1)
Time in department (mean minutes)	242	256	-14 (-76 to 49)
Return visit within 7 days for withdrawal	1 (3%)	0	3% (-3 to 9%)
Return visit within 7 days for any reason	1 (3%)	3 (10%)	-7% (-20 to 5%)

Source: Klein LR. *Clin Toxicol*. 2019.

IM Olanzapine versus oral clonidine

Considerations	• Lack of blinding
	• Time to peak concentration
	  • Olanzapine (15-45 minutes)
	  • Clonidine (60-180 minutes)
	• Time to last opioid use was not specified
	• Medications taken prior to arrival

Source: Klein LR. *Clin Toxicol*. 2019.

Diarrhea – Loperamide

Mechanism of action: Inhibits peristalsis and prolongs transit time reduces fecal volume and increases viscosity through the opioid receptor

Dosing
- PO 4 mg, followed by 2 mg after each loose stool (max: 16 mg/day)

Administration and storage
- Administer with plenty of fluids to prevent dehydration
- Shake oral solution well before administering dose
- Store at room temperature

Monitoring
- Torsades de pointes
- Drowsiness or dizziness
- Discontinue if constipation, abdominal paid, abdominal distension, blood in stool or ileus develop
- Caution in hepatic impairment due to reduced first-pass metabolism – monitor for CNS toxicity

Counseling
- Do not take higher than recommended doses due to risk of torsades de pointes

Sources:
Loperamide. In: Lexi-Drugs, retrieved 05/09/2020.
Toce MS. *J Med Toxicol.* 2018.

Nausea – Ondansetron

Mechanism of action: 5HT3-receptor antagonist

Dosing
- PO/IV/IM: 4 mg (max: 16mg/dose)
- Dose adjust for hepatic impairment (maximum: 8 mg/day)

Administration and storage
- IM: undiluted
- IV push: undiluted over at least 30 seconds, preferably 2-5 minutes
- Orally disintegrating tablet: do not attempt to push tablet through the foil. Using dry hands, place tablet on tongue and allow to dissolve
- Protect from light, store at room temperature

Monitoring
- QT prolongation
- Serotonin syndrome (mental status changes, autonomic instability, neuromuscular changes, gastrointestinal symptoms, seizures)

Counseling
- May be taken with or without food

Source: Ondansetron. In: Lexi-Drugs, retrieved 05/09/2020.

Nausea – Metoclopramide

Mechanism of action: Dopamine receptor antagonist, 5HT3-receptor antagonist

Dosing

- IV 10 or 20 mg
- PO 10 mg every 4 to 6 hours as needed
- Renal dose adjustment for CrCl less than 40 ml/minute
- Avoid treatment for longer than 12 weeks due to risk of tardive dyskinesia

Administration and storage

- Avoid rapid IV administration of doses greater than 10 mg
- Doses greater than 10 mg must be diluted in 50 mL of compatible solution and given IVPB over at least 15 minutes
- Store vials at room temperature and protect from light

Monitoring

- Rapid IV administration may be associated with transient, but intense, feeling of anxiety and restlessness, followed by drowsiness
- Extrapyramidal symptoms generally acute dystonic reactions within the initial 24-48 hours at the usual adult dose. Generally reversible within 2 to 3 months following discontinuation
- Tardive dyskinesia (irreversible) risk increases with duration and total cumulative dose

Source: Metoclopramide. In: Lexi-Drugs, retrieved 05/09/2020.

Insomnia – Trazodone (off-label)

Mechanism of action: Inhibits serotonin reuptake and acts as a 5HT2a receptor antagonist. Blocks H1 and alpha 1-adrenergic receptors

Dosing
- PO 50 mg to 100 mg at bedtime
- Can increase up to 200 mg at bedtime bases on response and tolerability

Administration and storage
- Administer shortly after a meal or light snack
- Store at room temperature, protect from light

Monitoring
- BBW: suicidal thinking/behavior
- CNS depression
- Relatively low risk of QT prolongation
- Orthostatic hypotension
- Serotonin syndrome

Counseling
- Do not abruptly stop taking this medication

Source: Trazodone. In: Lexi-Drugs, retrieved 05/09/2020.

Insomnia - Diphenhydramine

Mechanism of action: H1-antagonist

Dosing
- PO 25 to 50 mg at bedtime for occasional use

Administration and storage
- Dose should be given 30 minutes before bedtime
- Store at room temperature
- Protect capsules and tablets from moisture. Protect oral solution from freezing and light.

Monitoring
- CNS depression

Counseling
- Do not use with other products containing diphenhydramine, even topical ones.
- May impair physical or mental abilities– caution when operating machinery or driving

Source: Diphenhydramine. In: Lexi-Drugs, retrieved 05/09/2020.

Part IV. Alcohol Use Disorder (AUD)

Under DSM-5, anyone meeting any 2 the following 11 criteria during a 12-mouth period receives a diagnosis of AUD

- Had times when you ended up drinking more, or longer than you intended?
- More than once wanted to cut down or stop drinking, or tried to, but couldn't?
- Spent a lot of time drinking? Or being sick or getting over the after effects?
- Experienced craving — a strong need, or urge, to drink?
- Found that drinking — or being sick from drinking — often interfered with taking care of your home or family? Or caused job troubles? Or school problems?
- Continued to drink even though it was causing trouble with your family or friends?
- Given up or cut back on activities that were important or interesting to you, or gave you pleasure, in order to drink?
- More than once gotten into situations while or after drinking that increased your chances of getting hurt (such as driving, swimming, using machinery, walking in a dangerous area, or having unsafe sex)?
- Continued to drink even though it was making you feel depressed or anxious or adding to another health problem? Or after having had a memory blackout?
- Had to drink much more than you once did to get the effect you want? Or found that your usual number of drinks had much less effect than before?
- Found that when the effects of alcohol were wearing off, you had withdrawal symptoms, such as trouble sleeping, shakiness, irritability, anxiety, depression, restlessness, nausea, or sweating? Or sensed things that were not there?

Source: American Psychiatric Association. DSM-V

AUD is a chronic relapsing brain disease characterized by an impaired ability to stop or control alcohol use despite consequences

88,000 people die from alcohol-related causes annually

15 million people had AUD in the United States in 2018

Source: https://www.niaaa.nih.gov/publications/brochures-and-fact-sheets/alcohol-facts-and-statistics, retrieved 05/12/2020.

MAT:
Alcohol Use Disorder

Disulfiram

Acamprosate

Naltrexone

Disulfiram can be initiated in patients who have gone through detoxification or are in the initial stage of abstinence

Mechanism of action: aldehyde dehydrogenase inhibitor

- When taken concomitantly with alcohol, there is an increase in acetaldehyde levels
- High acetaldehyde causes uncomfortable symptoms (flushing, throbbing in head and neck, vomiting, diaphoresis, etc)
- Intensity of reaction is generally proportional to the amount of disulfiram and alcohol ingested

Dosing

- PO 125 to 500 mg/day (average 250 mg daily)

Administration and storage

- Do not administer disulfiram if alcohol has been consumed within the prior 12 hours
- Morning administration is preferred, but may be given at bedtime if sedation is experienced
- Tablets may be crushed and mixed with liquids
- Store at room temperature, protect from light

Monitoring

- Hepatotoxicity

Disulfiram reaction can occur up to 14 days after taking disulfiram if alcohol is consumed

Counseling

- Avoid alcohol consumption or >12 hours prior to taking disulfiram.

Sources:
Disulfiram. In: Lexi-Drugs, retrieved 05/09/2020.
https://www.samhsa.gov/medication-assisted-treatment/treatment, retrieved 05/08/2020.

Acamprosate is indicated in patients with alcohol use disorder who are abstinent at treatment initiation

Evidence
- Efficacy has not been demonstrated in patients who have not undergone detoxification and not achieved alcohol abstinence prior to beginning treatment

Mechanism of action: not fully understood
- Structurally similar to GABA– appears to restore balance to GABA and glutamate activities which seem to be disrupted in alcohol use disorder

Dosing
- PO 666 mg three times daily
- Consider 666 mg twice daily in patients <60 kg
- Renal dose adjustment necessary
- Contraindicated in CrCl≤ 30 mL/min

Administration and storage
- Administer without regards to meals
- Tablets should be swallowed whole, do not crush or chew
- Store at room temperature

Monitoring
- CNS depression
- Suicidal thinking/behavior

Sources:
Acamprosate. In: Lexi-Drugs, retrieved 05/09/2020.
https://www.samhsa.gov/medication-assisted-treatment/treatment, retrieved 05/08/2020.

Oral and extended-release injectable naltrexone are indicated in patients who can abstain from alcohol before the initiation of treatment

Mechanism of action: pure mu opioid antagonist

Dosing
- PO 50 mg daily (some patients may require doses up to 100 mg/day)
- IM 380 mg once every 4 weeks

Administration and storage
- Tablet: store at room temperature
- Injection: store unopened kit in the refrigerator; kit can be kept at room temperature for ≤7 days prior to use
  - Do not freeze
  - Following reconstitution of the suspension, administer immediately
- Do not administer IV, SubQ or into fatty tissue

Monitoring
- Injection site reactions
- Suicidal thoughts/depression

Sources:
Naltrexone. In: Lexi-Drugs, retrieved 05/09/2020.
https://www.samhsa.gov/medication-assisted-treatment/treatment, retrieved 05/08/2020.

Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar)

- Validated 10-item assessment tool to quantify the severity of alcohol withdrawal syndrome and to monitor and medicate patients going through withdrawal

1. Nausea, vomiting
2. Tremor
3. Paroxysmal sweats
4. Anxiety
5. Agitation
6. Tactile disturbances
7. Auditory disturbances
8. Visual disturbances
9. Headache
10. Orientation

Severity Score

≤ 8	Mild
9-15	Moderate
> 15	Severe

Source: Bayard M. *Am Fam Physician*. 2004.

Overview of management of alcohol withdrawal

General care

- Address abnormalities in fluids, electrolytes and nutrition
- IV thiamine to prevent Wernicke's encephalopathy

Fixed-schedule versus symptom-triggered regimens

- Benzodiazepine-based

Fixed-schedule	Symptom-triggered
Benzodiazepines are administered at specific intervals Additional doses of the medication are given as needed based on severity of withdrawal	Medication is given only when the CIWA-Ar score is higher than 8 points

Source: Bayard M. *Am Fam Physician*. 2004.

Overview of management of alcohol withdrawal

Choice of agent

- Based on pharmacokinetics
  - Diazepam and chlordiazepoxide
    - Long-acting
    - Smoother withdrawal: rebound withdrawal less likely to occur
    - Caution in hepatic impairment
  - Lorazepam
    - Intermediate-acting
    - May be preferable in elderly patients and those with hepatic impairment

Source: Bayard M. *Am Fam Physician*. 2004.

Part V. Assessment

Pharmacist & Nurse Assessment: Question 1

Which of the following MAT agents is indicated for both OUD and AUD?

A. Buprenorphine
B. Acamprosate
C. Naltrexone
D. Disulfiram

Pharmacist & Nurse Assessment: Question 1 Response

Which of the following MAT agents is indicated for both OUD and AUD?

A. Buprenorphine
B. Acamprosate
C. Naltrexone
D. Disulfiram

Pharmacist & Nurse Assessment: Question 2

Which of the following is not FDA-approved to be used in MAT therapy for opioid use disorder?

A. Buprenorphine
B. Methadone
C. Naltrexone
D. Clonidine

Pharmacist & Nurse Assessment: Question 2 Response

Which of the following is not FDA-approved to be used in MAT therapy for opioid use disorder?

A. Buprenorphine
B. Methadone
C. Naltrexone
D. Clonidine

Pharmacist & Nurse Assessment: Question 3

You are going to give a patient a new medication, disulfiram.
You should counsel the patient that they may have a disulfiram reaction up to ___ (time) since the last alcoholic beverage.

A. 12 hours
B. 24 hours
C. 1 week
D. 2 weeks

Pharmacist & Nurse Assessment: Question 3 Response

You are going to give a patient a new medication, disulfiram.
You should counsel the patient that they may have a disulfiram reaction up to ___ (time) since the last alcoholic beverage.

A. 12 hours
B. 24 hours
C. 1 week
D. 2 weeks

Avoid alcohol consumption or >12 hours prior to taking disulfiram.
Disulfiram reaction can occur up to 14 days after taking disulfiram if alcohol is consumed

Pharmacist & Nurse Assessment: Question 4

PF is a 36-year-old pregnant female with a history of opioid use disorder. She expresses that she is looking to enroll in a medication-assisted treatment plan. She would like to know which of the medications would be safe for her to take during her pregnancy.

I. Methadone
II. Buprenorphine
III. Naltrexone

A. I and III
B. I and II
C. II and III
D. I, II, and III
E. None are safe to take during pregnancy

Pharmacist & Nurse Assessment: Question 4 Response

PF is a 36-year-old pregnant female with a history of opioid use disorder. She expresses that she is looking to enroll in a medication-assisted treatment plan. She would like to know which of the medications would be safe for her to take during her pregnancy.

I. Methadone
II. Buprenorphine
III. Naltrexone

A. I and III
B. I and II
C. II and III
D. I, II, and III
E. None are safe to take during pregnancy

Pharmacy Technician Assessment: Question 1

You are delivering metoclopramide for nausea related to opioid withdrawal. *Which of the following adverse events is generally permanent?*

A. Tardive dyskinesia
B. Extrapyramidal symptoms
C. QT prolongation
D. Anxiety

Pharmacy Technician Assessment: Question 1 Response

You are delivering metoclopramide for nausea related to opioid withdrawal. *Which of the following adverse events is generally permanent?*

A. Tardive dyskinesia
B. Extrapyramidal symptoms
C. QT prolongation
D. Anxiety

Rapid IV administration may be associated with transient, but intense, feeling of anxiety and restlessness, followed by drowsiness
Extrapyramidal symptoms generally acute dystonic reactions within the initial 24-48 hours at the usual adult dose. Generally reversible within 2 to 3 months following discontinuation
Tardive dyskinesia (irreversible) risk increases with duration and total cumulative dose

Pharmacy Technician Assessment: Question 2

Buprenorphine extended-release injection is being removed from the fridge. *What is the new expiration date or time you should affix to the product?*

A. 15 minutes after removal
B. 12 hours after removal
C. 7 days after removal
D. Expiration does not change after removal

Pharmacy Technician Assessment: Question 2 Response

Buprenorphine extended-release injection is being removed from the fridge. *What is the new expiration date or time you should affix to the product?*

A. 15 minutes after removal
B. 12 hours after removal
C. 7 days after removal
D. Expiration does not change after removal

Store in refrigerator, bring to room temperature before administration (~15 minutes)
Once removed to room temperature – discard after 7 days

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Thank you!

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