Understanding Opioid Use Disorder & Medication Assisted Treatment (MAT)

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Objectives

- Discuss the context of Medication Assisted Treatment
- Discuss the neurobiology of opioid use disorder
- Discuss the pharmacology of buprenorphine and naloxone
- Discuss the pharmacologic implications of the hospitalized patient with a substance use disorder
- Disclosures: None

Why "Medication Assisted Treatment" for Addiction?

- Three waves of opioid overdose deaths:
  - #1: Increased prescribing in the 1990s
  - #2: Increased overdose deaths involving heroin in 2010
  - #3: Increased overdose deaths involving synthetic opioids, specifically illicitly manufactured fentanyl, in combination with heroin, counterfeit pills and cocaine in 2013 [1]

Why "Medication Assisted Treatment" for Addiction?

- In 2018, 67,367 drug overdose deaths occurred in the U.S. [1]
  - 69.5% of 2018 drug overdose deaths involved synthetic opioid, other than Methadone [1]
- In 2018, 716 drug overdose deaths occurred in Oklahoma [1]
- The criminalization of drug use is associated with adverse health outcomes [2]

Definitions

The American Society of Addiction Medicine (ASAM) defines **addiction** as a treatable, chronic medical disease involving complex interactions among brain circuits, genetics, the environment, and an individual's life experiences. People with addiction use substances or engage in behaviors that become compulsive and often continue despite harmful consequences. Prevention efforts and treatment approaches for addiction are generally as successful as those for other chronic diseases. [3]

The Diagnostic and Statistical Manual of Mental Disorders, 5th Ed. (DSM-5) states "the essential feature of a **substance use disorder** *is a cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues using the substance despite significant substance-related problems.* [4]

*** Quick Quiz Question ***

- The American Society of Addiction Medicine (ASAM) defines addiction as which of the following? Select all that apply.
  - A. Treatable disease
  - B. Chronic disease
  - C. Disease with compulsive behaviors despite harmful consequences
  - D. Disease involving complex interactions among brain circuits, genetics, the environment and life experiences
  - E. All the above

DSM-5

- Opioid Use Disorder is one of 10 classifications of Substance Use Disorder
  - Opioid use disorder (OUD) is primarily diagnosed based on the history provided by the patient and a comprehensive assessment that includes a physical examination. [4]
  - Diagnostic Criteria – A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period: [4]

DSM-5

1. Opioids are often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
3. A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
4. Craving or a strong desire or urge to use opioids.
5. Recurrent opioid use resulting in a failure to fulfill major role obligations such as work, school or home.
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.
8. Recurrent opioid use in situations in which it is physically hazardous.

DSM-5

9. Continue opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
10. Tolerance, as defined by a need for markedly increased amounts of opioids to achieve intoxication or desired effect, or a markedly diminished effect with continued use of the same amount of an opioid.
11. Withdrawal, as manifested by the characteristic opioid withdrawal syndrome* or opioids or a closely related substance are taken to relieve or avoid withdrawal symptoms.

*Three or more, develop minutes or days after cessation of use or administration of an opioid antagonist after a period of use: Dysphoric mood, nausea/vomiting, myalgia, lacrimation, rhinorrhea, pupillary dilation, piloerection, sweating, diarrhea, yawning, fever, insomnia not otherwise explained.

DSM-5

- F11.10 – Mild (Presence of 2-3 symptoms) [4]
- F11.20 – Moderate (Presence of 4-5 symptoms) [4]
- F11.20 – Severe (Presence of 6 or more symptoms) [4]
  - In early remission – After full criteria for OUD were previously met, none of the criteria for OUD have been met for at least **3 months**, but for less than 12 months (Except for craving to use).
  - In sustained remission – After full criteria for OUD were previously met, none of the criteria for OUD have been met for **12 months** or longer (Except for craving to use).
  - On maintenance therapy – If taking a prescribed agonist (methadone or buprenorphine) and none of the criteria for OUD have been met for that class of medication.

Predispositions

- Genetic factors account for about half of the likelihood that an individual will develop addiction. [3]
  - Environmental factors interact with the person's biology and affect the extent to which genetic factors exert their influence. [3]
  - Resiliencies the individual acquires (through parenting or later life experiences) can affect the extent to which genetic predispositions lead to the behavioral and other manifestations of addiction. [3]
  - Culture also plays a role in how addiction becomes actualized in persons with biological vulnerabilities to the development of addiction. [3]

Predispositions

- Other factors such as the disruption of healthy social supports and problems in interpersonal relationships which impact the development of resiliencies increase the likelihood of addiction. [3]
  - Exposure to trauma or stressors that overwhelm an individual's coping abilities [3]
  - Distortion in meaning, purpose and values that guide attitudes, thinking and behavior [3]
  - Distortion in a person's connection with self, with others, and with the transcendent (referred to as God by many, the Higher Power by 12-steps groups, or higher consciousness by others) [3]
  - The presence of co-occurring psychiatric disorders in persons who engage in substance use or other addictive behaviors. [3]

The A-B-C-D-E Harbingers of Addiction

A – Inability to **Abstain**

B – Impairment in **Behavioral** control

C – **Craving** or increased "hunger" for drugs or rewarding experiences

D – **Diminished** recognition of significant problems with one's behaviors and interpersonal relationships

E – A dysfunctional **Emotional** response

The Harbingers of Addiction

- Pearl:
  - A characteristic aspect of addiction is ***the qualitative way in which the individual responds to use***, not the quantity or frequency.
  - A particularly pathologic aspect is ***the preoccupation or obsession with or pursuit of rewards, despite the accumulation of adverse consequences***; as a reflection of ***impaired control***. [3]

The Neurobiology of Opioid Use Disorder

- Opiates are derived from poppy Papaver somniferum: Opium, Morphine, Codeine [5]
- Opioids are derived from opiates [5]
  - Semi-synthetic opiates: Heroin, Oxycodone, Hydrocodone, Hydromorphone [5]
  - Synthetic: Fentanyl, Meperidine, Methadone [5]

The Neurobiology of Opioid Use Disorder

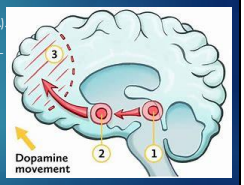
- Opioids & Opiates activate the Mu-opioid receptors in the body
  - Individuals have unique Mu receptor systems = variability in response
  - Mu receptors have a high affinity for morphine
- Agonist – A substance that promotes a receptor-mediated biologic response, often by competing with another substance at the same receptor.
- Partial-Agonist – A substance that promotes a receptor-mediated biologic response, but not with the efficiency of the agonist.
- Antagonist – A substance that interferes with the physiologic action of another, especially by combining with, and blocking its receptor.

The Neurobiology of Opioid Use Disorder

Opioids trigger dopamine release in the Mesolimbic Pathway – a reward / reinforcement pathway in the mid-brain.

1. Neurons originate in the Ventral Tegmental Area (VTA).
2. Neurons terminate in the Nucleus Accumbens (NAc) – NAc is stimulated by the release of dopamine to the receptors. [6]
3. NAc has projections into the Prefrontal Cortex where decisions are made about behaviors.

This is a dopaminergic system and is highly reinforcing. Dopamine is a neurotransmitter that is involved in pleasure, reward, motivation and emotional arousal. These reinforce life-sustaining activities such as food, water, exercise activities and sex. [7]



The Neurobiology of Opioid Use Disorder

Opioid use over time leads to long-lasting changes in the reward circuitry by hijacking the dopamine reward pathway and triggering up to 1000 times the normal amount of dopamine release in the brain. [8]

The Neurobiology of Opioid Use Disorder

- Heroin is highly lipophilic, and rapidly crosses the blood-brain barrier so it is the preferred injectable opioid over morphine, and highly addictive.[7]
  - The faster a substance occupies the receptor, the more euphoria
- Fentanyl is 50-100 times more potent than Heroin, Oxycodone, Marphine
  - Often added to other drugs to increase the addictive properties
- Codeine syrup – often mixed with alcohol or sedatives
- Hydrocodone (Norco, Vicodin, Lorcet, Lortab)
- Hydromorphone
- Meperidine
- Methadone
- Morphine
- Oxycodone
- Oxymorphone

*** Quick Quiz Question ***

- Opioid use over time leads to long-lasting changes in the reward circuitry in the brain. Which factors below contribute to this phenomena? Select all that apply.

  A. By hijacking the the dopamine reward pathway

  B. By triggering up to 1000 times the normal dopamine release in the brain

  C. Heroin is highly lipophilic and rapidly crosses the blood-brain barrier – the faster a substance occupies a receptor, the more euphoria is realized

  D. Fentanyl is 50-100 times more potent that heroin and is often added to other drugs to increase their addictive properties

  E. All the above

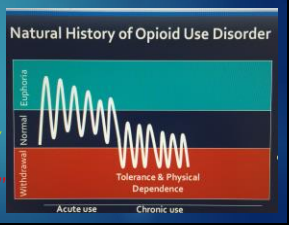
The Neurobiology of Opioid Use Disorder

Both tolerance and physical dependence are physiologic adaptations to chronic opioid exposure [7]

Tolerance – Increased dose needed to produce specific effect [8]

Physical dependence – Signs and symptoms of withdrawal by abrupt cessation, rapid dose reduction or administration of an antagonist [8]

"I have to take it to feel normal"

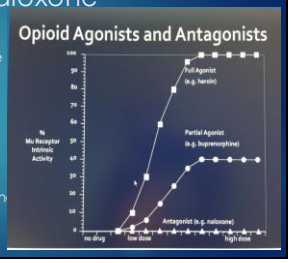


The Pharmacology of Buprenorphine and Naloxone

Full Opioid Agonist – Morphine, Heroin, Oxycodone, Hydromorphone, Codeine
- Highly reinforcing / rewarding
- Ceiling effect at 100% [8]

Partial Opioid Agonist – Buprenorphine
- Less reinforcing / rewarding
- Ceiling effect at less than 100% [8]

Opioid Antagonist – Naloxone/Naltrexon
- Zero effect on opioid receptor
- Blocks or displaces opioid agonists
- No matter how much drug [8]



The Pharmacology of Buprenorphine and Naloxone

- Affinity is the strength with which a drug physically binds to a receptor [8]
  - Buprenorphine's affinity is very strong and **it will displace** full agonists like heroin or methadone
- Dissociation is the speed of disengagement of a drug from the receptor [8]
  - Buprenorphine's dissociation is slow

The Pharmacology of Buprenorphine and Naloxone

- Spontaneous Acute Opioid Withdrawal – Depends on the half-life of the drug [8]
  - Heroin – Onset 4-6, Peak ~ 3d, Duration 4-7d
  - Methadone – Onset 1-2d, Peak ~ 7d, Duration 12-14d
- Precipitated Acute Opioid Withdrawal – Antagonist or Partial Agonist
  - Naloxone – Onset - minutes, Peak - minutes, Duration ~ 20 minutes
  - Naltrexone – Onset – minutes, Peak – minutes, Duration 1-2d
  - Buprenorphine – Onset – minutes, Peak – minutes, Duration 1-2d

Buprenorphine Products

- Buprenorphine sublingual tab *Subutex brand discontinued in the U.S.
  - 2mg, 8mg
  - Monotherapy preferred during pregnancy
- Suboxone – Buprenorphine / Naloxone sublingual film
  - 2mg/0.5mg, 4mg/1mg, 8mg/2mg, 12mg/3mg
  - Generic available
- Zubsolv – Buprenorphine / Naloxone sublingual tab
  - 0.7mg/0.18mg, 1.4mg/0.3mg, 2.9mg/0.71mg, 5.7mg/1.4mg, 8.6mg/2.1mg, 11.4mg/2.9mg
  - Not bioequivalent to other products – see prescribing info
- Sublocade – Buprenorphine injectable
  - 100mg/5ml, 300mg/1.5ml SC q 26 – 30 days
- Bunavail – Buprenorphine / Naloxone buccal strip
  - 2.1mg/0.3mg, 4.2mg/0.7mg, 6.3mg/1mg
  - Not bioequivalent to other products – see prescribing info $$$

The Hospitalized Patient - Withdrawal

- Patients with a KNOWN substance use disorder
  - Methadone and Buprenorphine should not be abruptly withdrawn – continue dose as prescribed
  - S/S of withdrawal: Tachycardia, sweating, restlessness, dilated pupils, bone or joint aches, nasal stuffiness or rhinorrhea, tearing, N/V/D, tremor or muscle twitching, yawning, anxiety or irritability, piloerection
  - Consult with outpatient prescriber to develop a plan
    - Prescriber can be found on the Oklahoma PMP
    - https://oklahoma.pmpaware.net/identities/new

The Hospitalized Patient - Pain

- "Opioid Debt" – Patients with OUD & physical dependence on opioid agonist therapy (Methadone or Buprenorphine) must be maintained on a daily equivalence before any analgesic effect is realized with opioids used to treat acute pain. [8]
  - Active OUD = less pain tolerance than peers in remission [7]
  - PMH OUD = less pain tolerance than siblings without addiction history [8]
  - Current opioid maintenance treatment (Methadone, Buprenorphine) = less pain tolerance than matched controls [8]

The Hospitalized Patient - Pain

- Buprenorphine parenteral and transdermal approved for pain and not addiction treatment
  - Cannot be used off-label for addiction under Drug Addiction Treatment Act (DATA 2000). [8]
- Sublingual approved for addiction treatment and not pain
  - Can be used off-label for pain. [8]
  - DEA X-Number required for prescribing
- Analgesic effect of SL buprenorphine 0.2-0.8mg q6-8h in opioid naïve post-op pain [8]
  - CNS and respiratory depression ceiling effect documented, no data on analgesic ceiling effect [8]

The Hospitalized Patient - Caution

- Avoid concurrent use of benzodiazepines
  - Among the 34 reported buprenorphine-associated overdoses in France, 31 also had benzodiazepines [8]
- Buprenorphine undergoes hepatic metabolism, primarily by the CYP4503A4 system
  - Impaired hepatic function should be monitored, but buprenorphine can be prescribed without major concern for liver injury. [8]
- Monitor: LFTs at baseline, EKG if QT prolongation, BP, s/s respiratory depression

The Hospitalized Patient – Pregnancy

- Buprenorphine monotherapy recommended [7]
- Naloxone is not recommended, except in life-threatening overdose [7]
- Maintenance therapy has been shown to increase retention in prenatal care, addiction recovery and in-hospital deliveries [8]
- 70% reduction in OD related deaths, decrease risk of HIV, HBV, HCV [8]
- Decrease in intrauterine fetal demise, intrauterine growth restriction, preterm deliveries [8]
- Labor and Delivery – Continue maintenance dose and epidural only (Commonly used Stadol or Nubain are agonist/antagonist and can precipitate withdrawal) [8]
- Post C-Section – Continue maintenance dose and IV NSAIDS and full opioid agonists [8]

The Hospitalized Patient – Pregnancy

- Neonatal Abstinence Syndrome (NAS) – Generalized disorder with dysfunction of the autonomic nervous system, GI tract and respiratory system [8]
  - 60-80% of neonates with intrauterine exposure to opioids [8]
  - Onset: Within 72 hours after delivery [8]
  - Duration: Up to 4 weeks [8]
  - Treatment: Diluted tincture of opium (DTO), oral morphine, methadone [8]
    - Non-pharmacologic – Breastfeeding, skin-to-skin, swaddling, low stimulation environment, maternal rooming-in [8]
  - Meta-analysis of 12 studies 1996-2012 – Buprenorphine exposed neonates had shorter NAS treatment duration and lower morphine dose [8]
- Buprenorphine amount in breastmilk is small and has poor oral bioavailability. [8]
  - 30% decrease in the development of NAS, 50% decrease in neonatal hospital stay [8]
- Buprenorphine monotherapy has higher risk for diversion [8]

Office Based Therapy (OBT)

Opioid use disorder is a chronic, relapsing disease, which has significant economic, personal and public health consequences [7]

- Naloxone therapy alone is ineffective due to non-adherence [7]
- Opioid withdrawal management alone is not a treatment method [7]
- Medication for opioid withdrawal management is recommended over abrupt cessation, which may lead to strong cravings and continued use [7]
- Psychosocial treatment should be implemented in conjunction with buprenorphine [6] (Individual therapy, links to family support, community resources; groups, 12-Step meetings)
- Steps to avoid diversion – frequent visits, confirmatory UDS, random pill counts [7]
- Naloxone kits are readily available in the community, and prescriptions should be provided to patients being treated and their family members / significant others [7]

The Outpatient - Vignette

- Precious Johnson – 36y, BF, last visit 10/10/18
  - CC: "Trouble sleeping and headaches"
    - HPI: Problems sleeping for several months because of headaches. Also reports toothache. Describes symptoms as "unbearable headaches." "I need some help to get some medicine. I can't go without the pain medicine and don't know have anywhere else to go, you have to help me."
    - Pmh: Hypertension, obesity, perimenopause – LMP August 2020, irregular since 2017
    - Meds: HCTZ 25mg QD, Lisinopril 10 mg QD – out of meds >1y. Currently taking Tor tab 10mg QID for dental pain
      - Allergies: NSAIDs
    - Social: denies tobacco, alcohol, illicit drugs. Single mom of 4 – ages 18, 15, 13, 8. She lost her job and insurance in 2019. She lost her apartment and parents have moved her children into their house. She is staying with friend and has not seen her kids since August.
    - Family: Father: HTN, DM, alcoholism – sober x10y. Mother: Obesity, HTN, alcoholism – sober x10y. Sister: HTN, deceased at age 23 of heroin overdose. Children: healthy, oldest son is in Juvenile Justice custody for burglary.
    - ROS: Confirms headaches daily, runny nose, watery eyes, sleeps <1-2 hours during the day, unable to sleep at night, confirms episodes of sweating and nervousness, feels anxious and restless "most of the time" and body aches daily. Nausea and diarrhea 3-4 times per week.

The Outpatient - Vignette

- PE:
  - Vital signs: 169/98, 110, 16, 93%, 5'6", 46.4kg, BMI: 16.5
  - General: Thin, hair is unkempt, clothing is inappropriate for cold windy weather today. Frequent yawning, crying
  - HEENT: Normocephalic, Pupils 3+, lacrimation, rhinorrhea, TMs pearly, turbinates boggy and erythematous, posterior pharynx clear, Tonsils 1+
  - Neck: Supple, nontender, no masses, no JVD, no bruits
  - Chest: Symmetric, nontender
  - Pulmonary: Normal effort, lungs clear bilaterally, no dullness
  - Cardiovascular: Heart tones distinct, regular rate, rhythm, extremities warm, 2+ peripheral pulses
  - Gastrointestinal: Abdomen soft, nontender, active bowel sounds
  - Musculoskeletal: Gait steady, grip strong, straight leg raises appropriate for age and uniform, joints nontender
  - Skin: Piloerection, diaphoretic, no rash, wounds or lesions
  - Lymph: No masses or tenderness in cervical, axillary, epitrochlear or inguinal
  - Neurological: Fine tremor in extremities, CNI-XII intact, DTR in bilateral upper and lower extremities 2+
  - Psychological: Alert, oriented to person, place, time and situation, irritable, flat affect, speech is expansive, [illegible] about drug seeking behaviors, Obsessive about explaining pain and inability to sleep; Defensive when asked about drug seeking sources and use
  - PMP: Hydrocodone/Acet 10mg #40, Bob Smith DDS 11/10/20, 11/1/20, 10/15/20, 10/1/20, 9/16/20, 7/10/20

The Outpatient - Vignette

- Assessment:
  - Opioid Withdrawal due to opioid use disorder
  - Hypertension
  - Underweight
  - Perimenopause
- Plan:
  - Labs – CBC, CMP, TSH, UA, BHCG, toxicology
  - Refer to Outpatient Substance Use Treatment
  - Schedule pap
  - Restart lisinopril
  - f/u 1 week

*** Quick Quiz Question ***

- What are the harbingers of addiction that we see during the Outpatient Vignette visit? Select all that apply.
  - A. Inability to Abstain
  - B. Impairment in Behavior control
  - C. Craving or increased hunger for rewarding experiences
  - D. Diminished recognition of significant problems with one's behaviors and interpersonal relationships
  - E. Dysfunctional emotional response
  - F. All the above

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Questions?

Galveston, 2017