Contributions and Consequences of the Opioid Crisis, and Modes of Treatment for Opioid-Use Disorder

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Disclosures

- I have no financial relationships or commercial interests to disclose for this presentation

Learning Objectives

- Review factors that have contributed to the opioid crisis
- Describe medications currently available for Medication-Assisted Therapy (MAT) for the treatment of opioid use disorder
- Differentiate myths from facts related to MAT

Read All About It!

"Just as there is no single cause and no single party responsible for the opioid epidemic, there is no single solution"- US Chamber of Congress

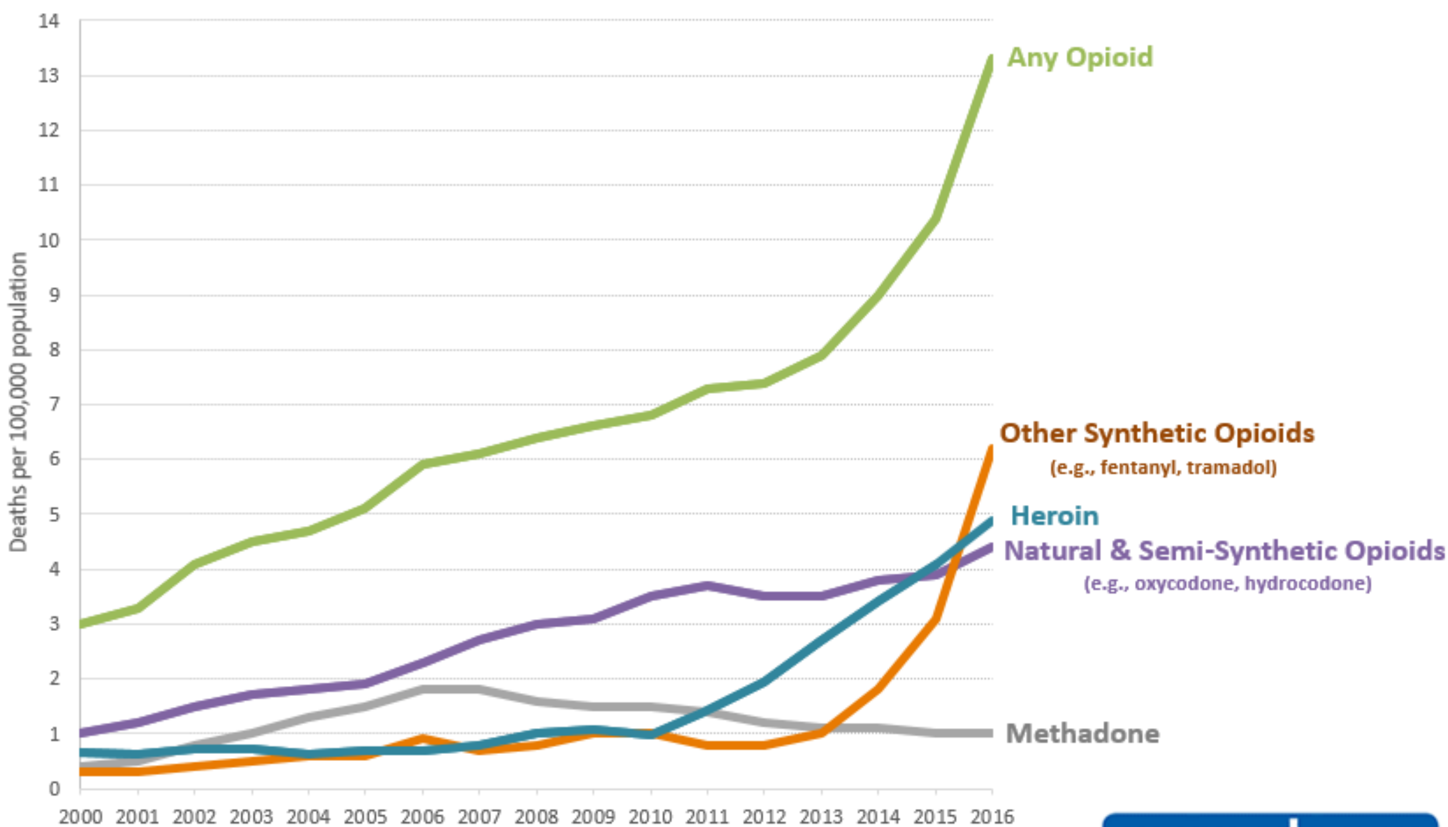
"An estimated 1 out of 5 patients with non-cancer pain or pain-related diagnoses are prescribed opioids in office-based settings"- M Daubresse, Medical Care 2013

"US overdose deaths from fentanyl and synthetic opioids doubled in 2016"- The Guardian

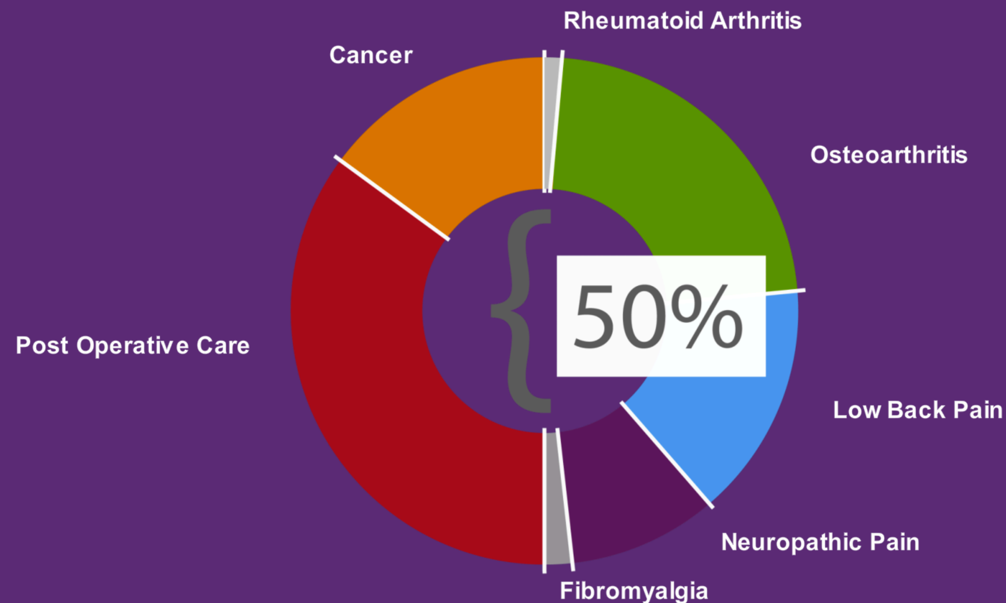
"The opioid crisis has cost the country approximately $504 billion, equivalent to 2.8 percent of the year's GDP, in 2015"- C. Leins, US News

"The Opioid Epidemic: A Crisis Years in the Making"- M. Salam, New York Times

Opioid Epidemic



Who is Prescribed Opioids?



Roadmap to Crisis

- 1980-90's
  - Improvements in treating cancer and postsurgical pain
  - Aggressive pharmaceutical marketing with new long-acting opioids
  - Opioid use was encouraged by implementation of the "5th vital sign" and through patient satisfaction surveys
- 2000's
  - Prescribers viewed that long-term opioids were beneficial for treating chronic non-cancer pain and that addiction was no longer a concern
  - The Joint Commission 2001 standard implemented an assessment and management of pain in hospitals and other health care settings

Contributions within the Medical Community

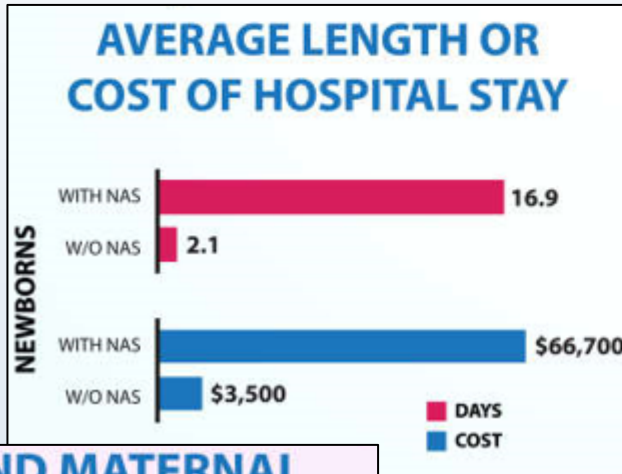
- Inadequate training across the continuum of medical education.
- Lack of access to multimodal pain care
- Limited and inadequate payment for non-pharmacological approached to pain management.

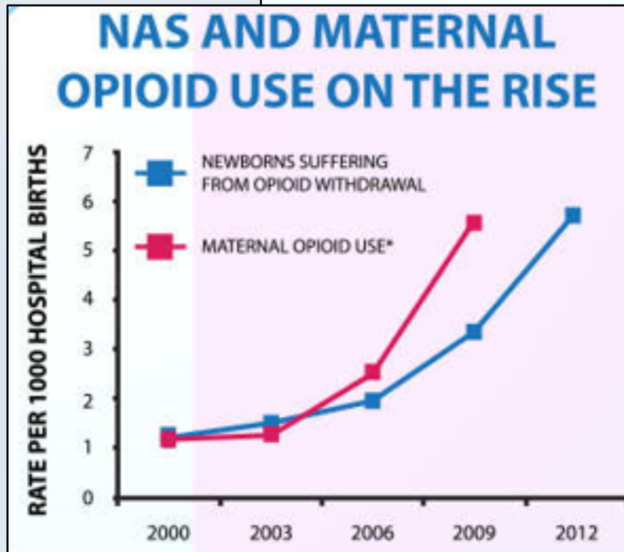
Impact & Consequences

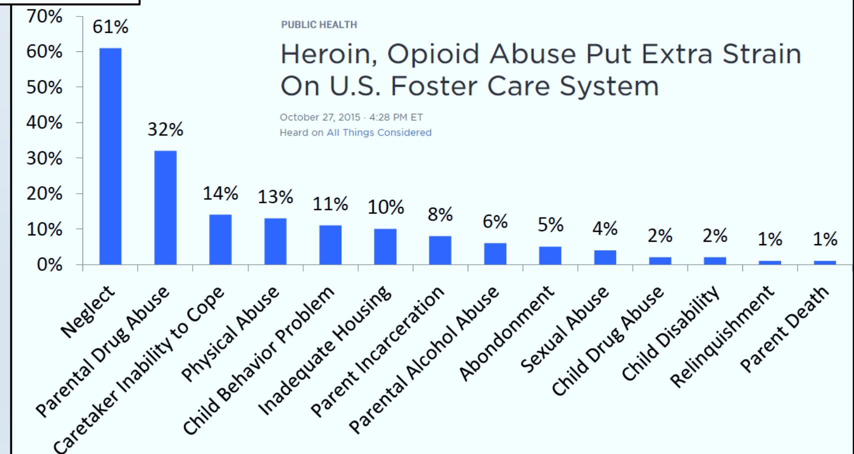
- Increased emergency department visits
- Increased number of opioid use disorders
- Increased hospital admissions
- Contributed to a resurgence of heroin addiction
- Increased number of deaths due to overdose

American Medical Association. A Primer on the Opioid Morbidity and Mortality Crisis: What Every Prescriber Should Know. CME. Accessed July 2018. https://cme.ama-assn.org/activityV2/4896593#!/activity

Impact & Consequences







Source:
https://www.acf.hhs.gov/sites/default/files/cb/afcarsreport23.pdf
Patrick et al., JAMA 2012, Patrick et al Journal of perinatology 2015

Which of the following statements are correct?

A. The opioid epidemic is an acute problem
B. Opioid overdoses are only due to street drug misuse
C. CDC reports show that opioids are only prescribed for the treatment of post-operative and cancer pain
D. Health care providers have contributed to the opioid crisis.
E. All of the above

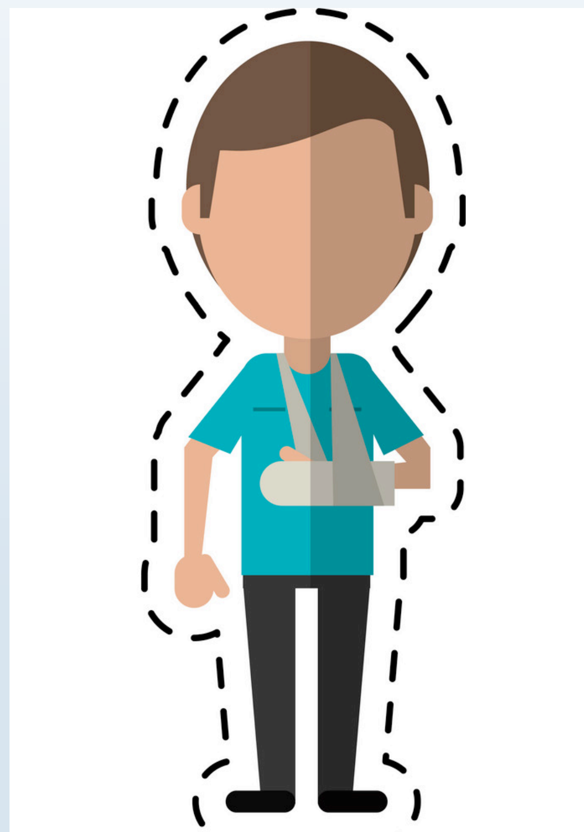
Opioid-Use Disorder (OUD)

- Chronic, relapsing brain disease
- Develops gradually over time with repeated use due to changes in the brain
- 4 C's of Addiction
  - Craving
  - Loss of Control
  - Compulsion to use
  - Continued use despite Consequences

Screening Patients for OUD

Patient Factors

- Gender
  - Caucasian
  - Male
  - Low income
  - Rural setting
- Patient history
  - Previous substance abuse disorders
  - Mental health diagnosis



Screening Patients for OUD

<u>Prescribing Factors</u>

- Higher average daily dose
- Long acting opioids
- Concomitant benzodiazepines
- Multiple prescribers
- Concurrent overlapping opioid prescriptions

The Comprehensive Addiction & Recovery Act (CARA)

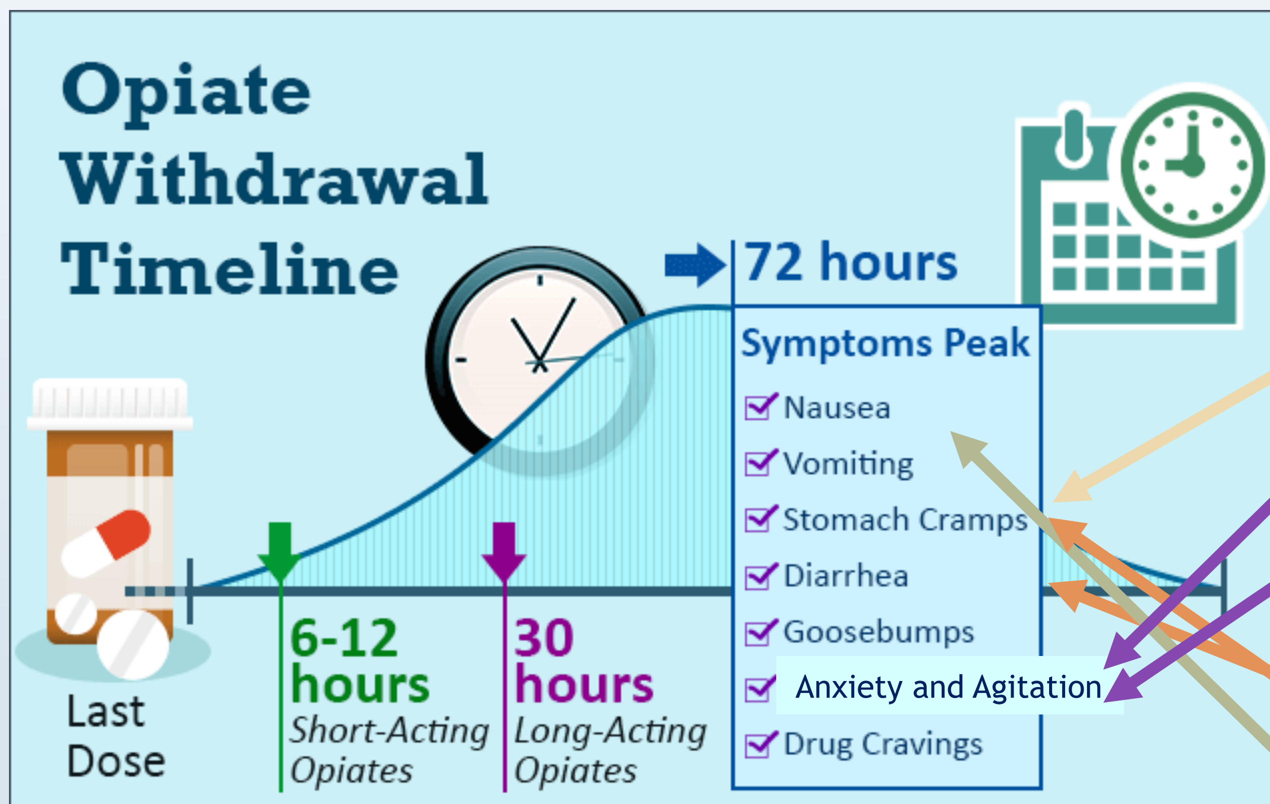
- Passed in 2016
- Authorized over $181 million each year in new funding to fight the opioid epidemic
- Goals
  - Improve education and prevention efforts to prevent the abuse of methamphetamines, opioids, and heroin
  - To promote treatment and recovery
  - Make naloxone available to law enforcement agencies and other first responders to help in the reversal of overdoses
  - Strengthen and increase the use of Prescription Drug Monitoring Programs

https://cadca.org/comprehensive-addiction-and-recovery-act-cara

Prescription Drug Monitoring Program (PDMP)

- State-run programs
- Allows registered health-care professionals to identify high-utilizers of controlled substances by ;
  - Identifying "Doctor Shoppers"
  - Listing all recently filled prescriptions
  - Reporting potentially dangerous drug combinations (i.e., benzodiazepines and opioids)
- See for yourself!
  - Mississippi State PDMP

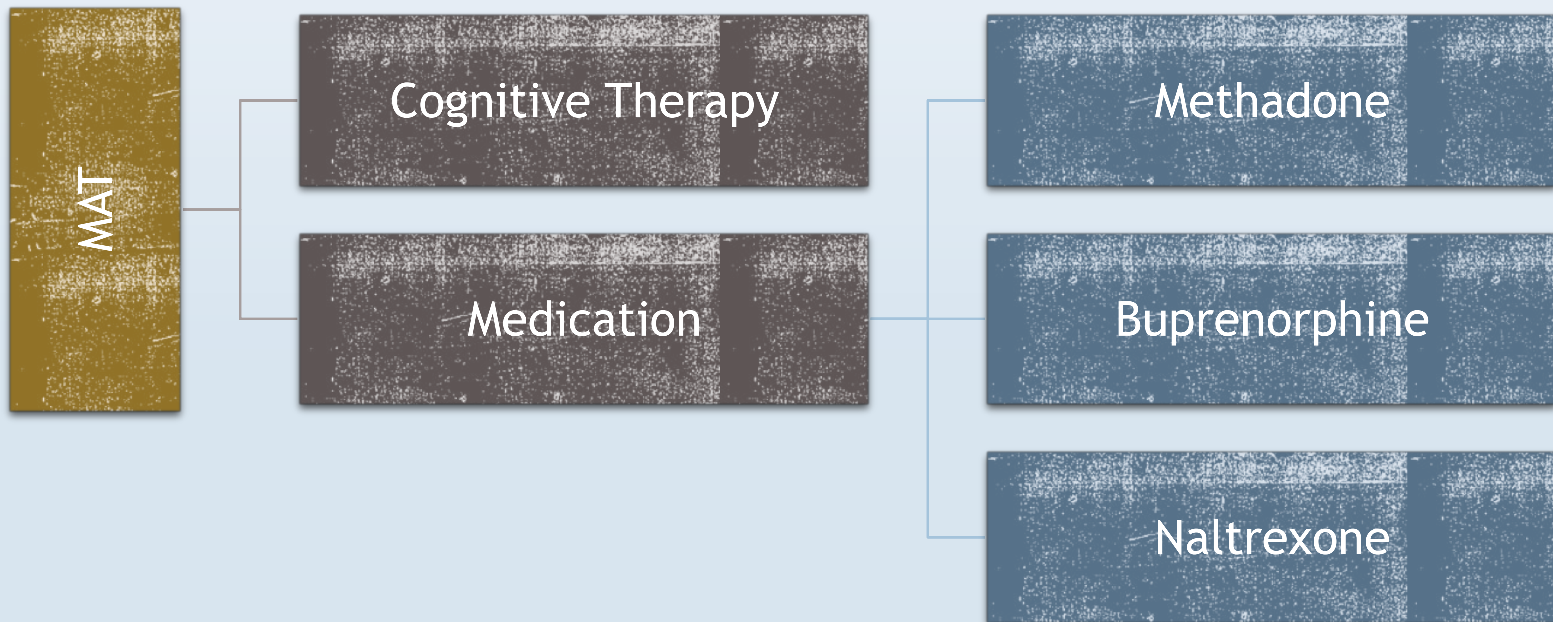
Initial Treatment



- Acetaminophen or NSAIDS
- Benzodiazepines
- Clonidine
- Loperamide
- Ondansetron

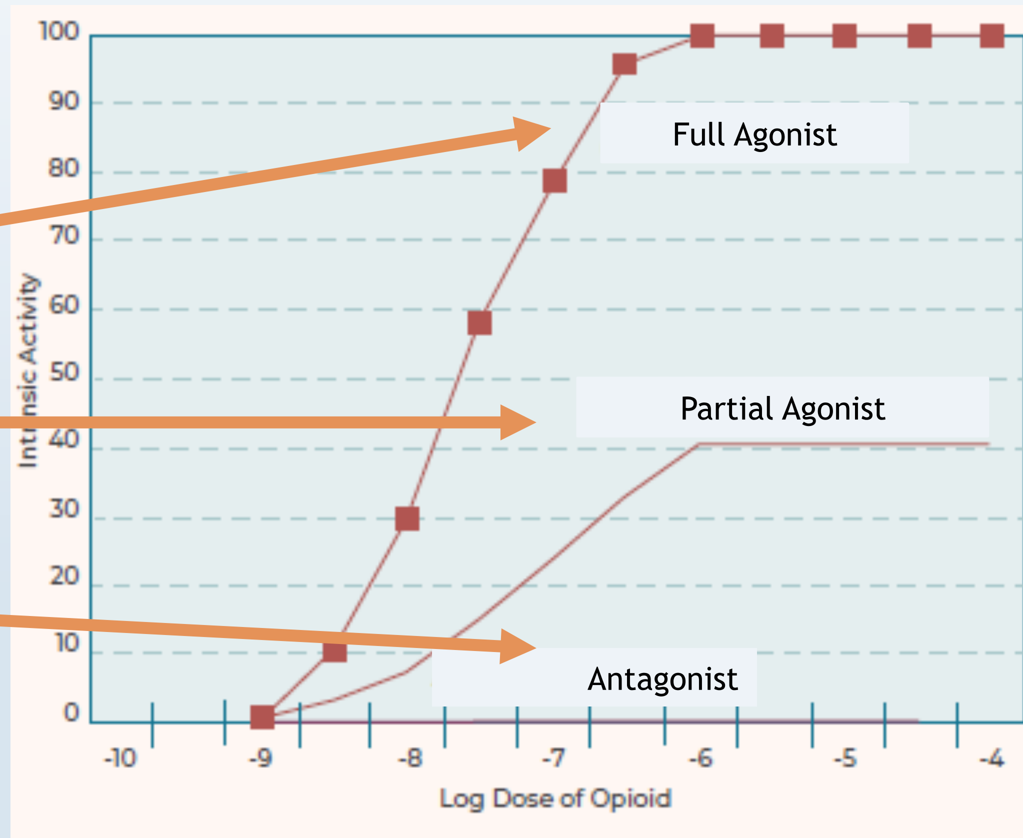
Medication-Assisted Treatment (MAT)

- “The use of medications, in combination with counseling and behavioral therapies, to provide a 'whole-patient' approach to the treatment of substance use disorders" - SAMHSA



Center for Substance Abuse Treatment. Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs. Treatment Improvement Protocol (TIP) Series 43. HHS Publication No. (SMA) 12-4214. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2005.

Medication-Assisted Treatment (MAT)



Treatment Overview

	Methadone	Buprenorphine	Buprenorphine /Naloxone	Naltrexone
Activity	Full Agonist	Partial Agonist	Combination	Antagonist
Schedule	II	III	III	n/a
Restrictions	OTP	Certified prescriber	Certified prescriber	None
Uses	Withdrawal and Treatment	Withdrawal and Treatment	Withdrawal and Treatment	Treatment
Formulations	Tablet or liquid	Tablet, buccal film, or XR-implant	Tablet or buccal film	Tablet or XR-injection

Medication Assisted Therapy (MAT)

Morbidity & Mortality
Overdose Deaths
Transmission of ID
Criminal Activity

Social Functioning & Retention

Methadone Overview

- Most used and widely studied medication-assisted treatment
- Studies support that methadone;
  - Decreases or eliminates illicit opioid and heroin use
  - Reduces the potential transmit infectious diseases
  - Decreases criminal activity
  - Improves maternal and fetal outcomes for women who are pregnant or breastfeeding.
  - Increases treatment retention
- No ceiling effects

Mattick, R. P., (2009) *Cochrane Database of Systematic Reviews, 8*(3)
Connock, M.(2007). In: NIHR Health Technology Assessment programme: Executive Summaries. Southhampton, UK: *NIH Journals Library*.
Mattick, R. P., (2003).Buprenorphine versus methadone maintenance therapy: A randomized double-blind trial with 405 opioid-dependent patients. *Addiction*, 98,

Methadone Dosing

- Dosing
  - Generally starts at 30-40 mg daily
  - Doses upwards of 120-180 mg daily
- Daily observed medication administration
- Better for patients
  - Who need structure of observation
  - Have a high “opioid debt”
  - Who have used high doses (heroin addicts)

Center for Substance Abuse Treatment. Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs. Treatment Improvement Protocol (TIP) Series 43. HHS Publication No. (SMA) 12-4214. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2005.

Methadone Pharmaco-highlights

- Pharmacokinetics
  - Wide variability in pharmacokinetics
    - T ½= 8-59 hours!
  - Drug interactions are significant due to metabolism through CYP3A4, 2B6 and 2D6.
    - Antiretroviral agents and tuberculosis treatment increase metabolism
    - SSRIs decrease metabolism
- Side Effects and Precautions
  - QTc prolongation >30mg/day
  - Respiratory depression
  - Sedation

Buprenorphine Overview

- Studies show that Buprenorphine maintenance can;
  - Decrease or eliminate opioid use (including heroin)
  - Increase overall well-being and social functioning
  - Reduce cravings
  - Reduce withdrawal symptoms
  - Increase treatment retention
  - Reduce potential to contract infectious disesases
  - Decrease mortality

Substance Abuse and Mental Health Services Administration. (2016). *Buprenorphine*. Washington, DC: Department of Health and Human Services. Retrieved from http://bit.ly/1PC4cg7

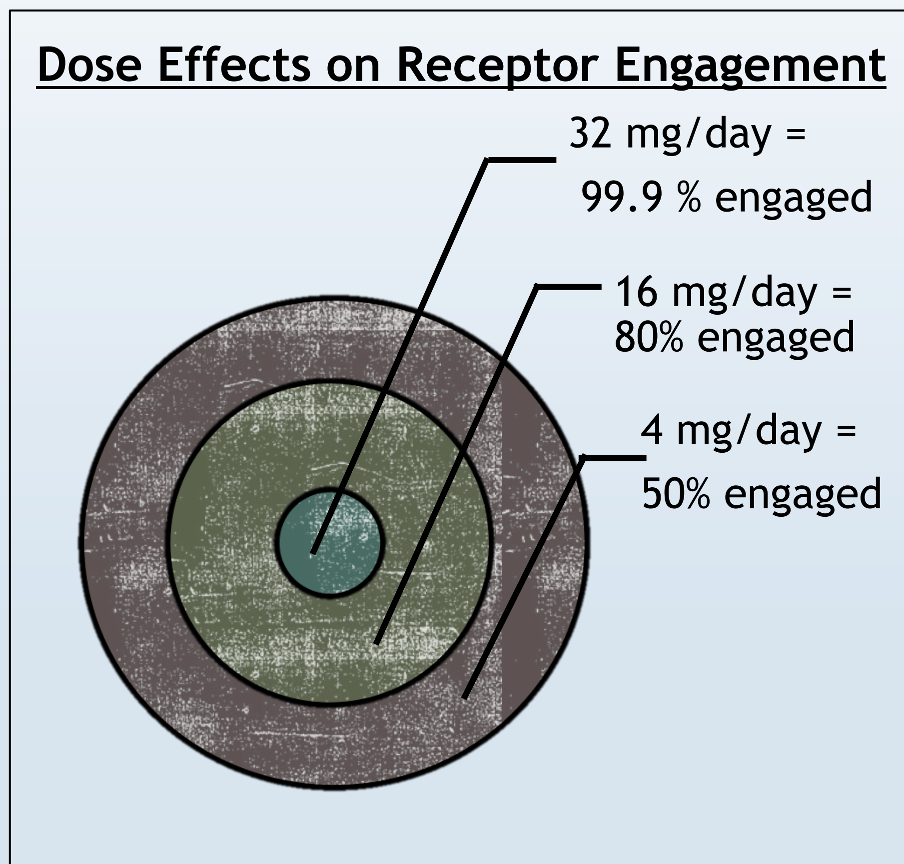
Buprenorphine Binding

- Receptor Binding
  - Semisynthetic, partial mu-receptor agonist
    - Ceiling effect to euphoria, respiratory depression, sedation
    - Significantly less potential for overdose
  - Kappa and delta-receptor antagonist
    - Less dysphoria
- Competitors
  - Approximately, 30x more potent than morphine that produces analgesia at low receptor occupancy (5-10%)
  - Sublingual doses of buprenorphine (16mg) can reduce mu-receptor binding of opioids by 80%

ASAM National Practice Guideline.2015
Hannery, H. S. (2015). Medication-assisted treatment of opioid use disorder: review of the evidence and future directions. *Harvard review of psychiatry*, *23*(2), 63-75.

Buprenorphine Dosing

- Common Regimen
  - 4 mg/day = prevent withdrawal symptoms
  - 16mg/day = block cravings
  - Max dose= 24-32 mg/day
- Parenteral and transdermal formulations approved for pain, ***not*** addiction treatment
- Sublingual formulation approved for addiction, ***not*** pain treatment



Buprenorphine Pharmaco-Highlights

- Time to Peak= 40 minutes to 3.5 hours
- $T_{1/2}$= 3-44 hours
- CYP3A4 metabolism
- Side Effects
  - Constipation
  - Nausea
  - Precipitated withdrawal

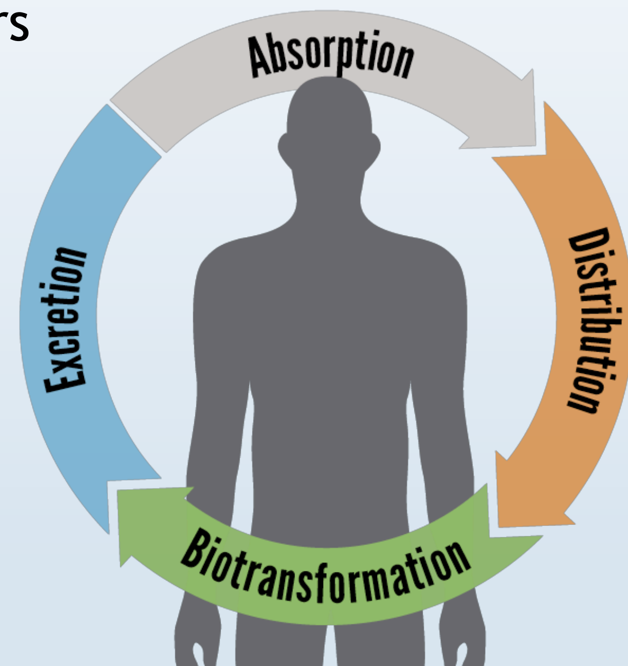
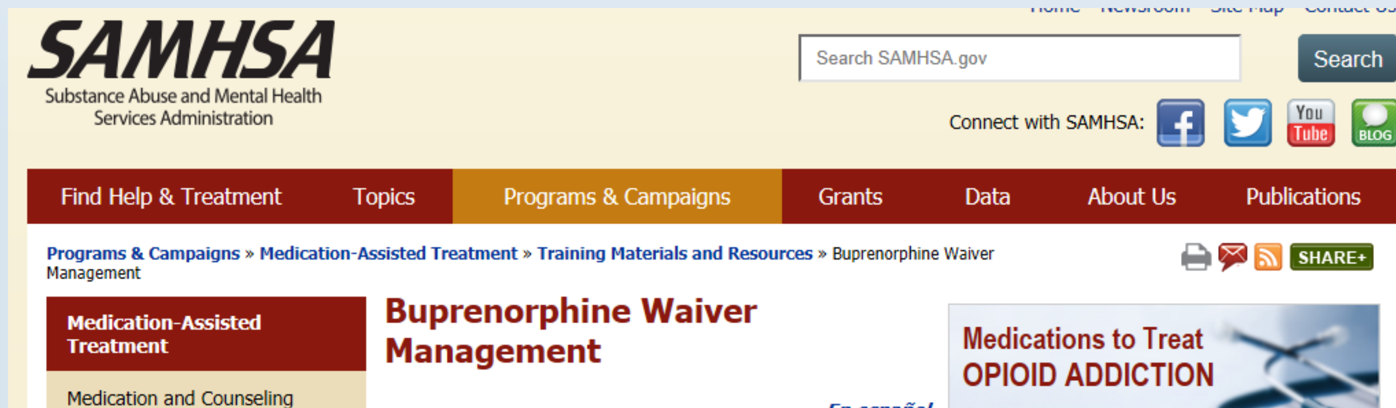


Image from: https://biolaurus.com/imaging-pharmacokinetics/

Drug Addiction Treatment Act of 2000 (DATA 2000)

- Expands the clinical context of medication-assisted opioid dependency treatment
- Qualified prescribers (MD, NP, and PAs etc.) are permitted to dispense/prescribe CII-V substances in settings other than an opioid treatment program
- Online Courses available from SAMHSA



Naltrexone

- Blocks euphoria of opioid drugs
- For the treatment of alcohol abuse and opioid use disorder
- Higher affinity for these receptors than has heroin, morphine, or methadone, thus blocks the effects
- Studies have indicated very high (70 to 80 percent) dropout rates from naltrexone therapy

Stine et al. 2003

Which of the following is the correct pairing for buprenorphine?

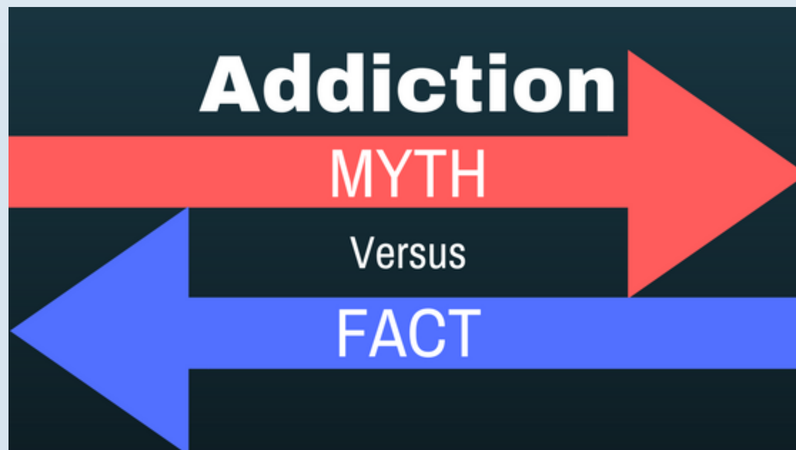
A. Full agonist, no ceiling effect
B. Partial agonist, ceiling effect
C. Antagonist, no ceiling effect
D. Partial antagonist, ceiling effect

Myths About Medication-Assisted Treatment

- **Myth #1: Trades one addiction for another**

“Use of FDA-approved medications in combination with evidence-based therapies can be effective in the treatment of addiction and may **help recovering users stay in treatment longer**, extending periods of sobriety and paving the way for successful recovery”

-SAMHSA



Myths About Medication-Assisted Treatment

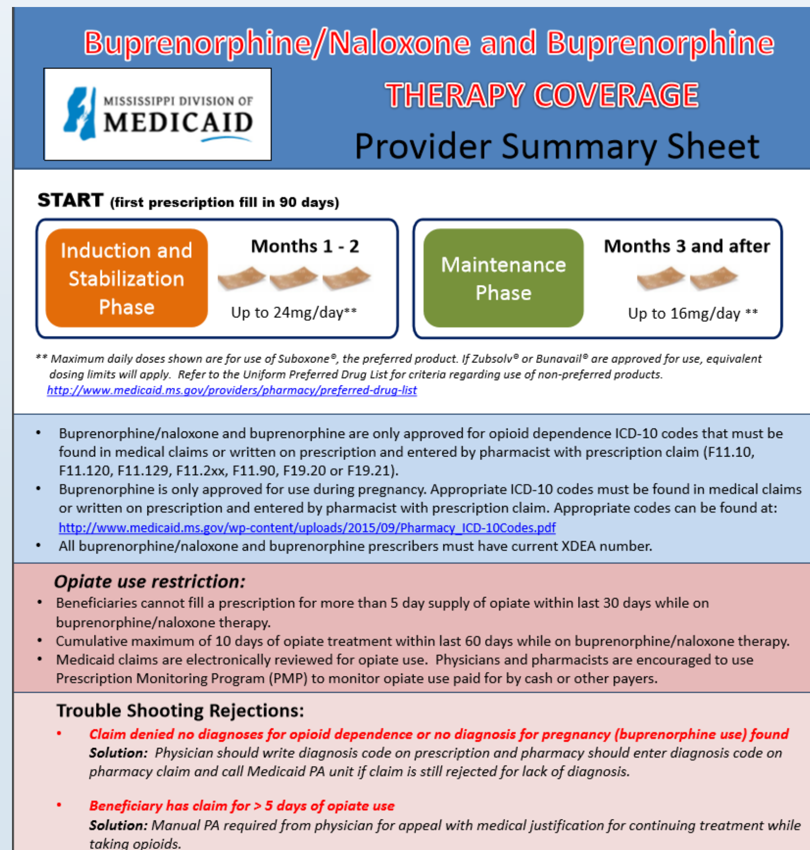
- **Myth #2: For only the most severely addicted patients**

1. Have an official diagnosis of an addiction to alcohol or opioids
2. Be willing to fully comply with prescribing instructions
3. Lack physical health issues that the medication could possibly exacerbate
4. Be fully educated on alternative options.

Myths About Medication-Assisted Treatment

- Myth #3: Treatment is not covered by insurance

Mississippi Medicaid- Buprenorphine



Buprenorphine/Naloxone and Buprenorphine

THERAPY COVERAGE

Provider Summary Sheet

MISSISSIPPI DIVISION OF MEDICAID

START (first prescription fill in 90 days)

Induction and Stabilization Phase	Months 1 - 2 Up to 24mg/day**

Maintenance Phase	Months 3 and after Up to 16mg/day **

*** Maximum daily doses shown are for use of Suboxone®, the preferred product. If Zubsolv® or Bunavail® are approved for use, equivalent dosing limits will apply. Refer to the Uniform Preferred Drug List for criteria regarding use of non-preferred products.*
http://www.medicaid.ms.gov/providers/pharmacy/preferred-drug-list

- Buprenorphine/naloxone and buprenorphine are only approved for opioid dependence ICD-10 codes that must be found in medical claims or written on prescription and entered by pharmacist with prescription claim (F11.10, F11.120, F11.129, F11.2xx, F11.90, F19.20 or F19.21).
- Buprenorphine is only approved for use during pregnancy. Appropriate ICD-10 codes must be found in medical claims or written on prescription and entered by pharmacist with prescription claim. Appropriate codes can be found at: http://www.medicaid.ms.gov/wp-content/uploads/2015/09/Pharmacy_ICD-10Codes.pdf
- All buprenorphine/naloxone and buprenorphine prescribers must have current XDEA number.

Opiate use restriction:

- Beneficiaries cannot fill a prescription for more than 5 day supply of opiate within last 30 days while on buprenorphine/naloxone therapy.
- Cumulative maximum of 10 days of opiate treatment within last 60 days while on buprenorphine/naloxone therapy.
- Medicaid claims are electronically reviewed for opiate use. Physicians and pharmacists are encouraged to use Prescription Monitoring Program (PMP) to monitor opiate use paid for by cash or other payers.

Trouble Shooting Rejections:

- ***Claim denied no diagnoses for opioid dependence or no diagnosis for pregnancy (buprenorphine use) found***
  Solution: *Physician should write diagnosis code on prescription and pharmacy should enter diagnosis code on pharmacy claim and call Medicaid PA unit if claim is still rejected for lack of diagnosis.*

- ***Beneficiary has claim for > 5 days of opiate use***
  Solution: *Manual PA required from physician for appeal with medical justification for continuing treatment while taking opioids.*

True or False: MAT should be used for patients that are not yet committed to stopping opioid use.

A. True

B. False

Treating Pain on MAT

Methadone

Continue daily therapy

Add different opioid for acute pain

Buprenorphine

Elective

D/c x several days prior to scheduled surgery, replace w/ methadone

Unplanned

stop buprenorphine and use IV opioid that binds well to μ receptors

Maximize adjunctive agents (acetaminophen, NSAIDs, muscle relaxants, etc…)

Treating Pain on MAT: Tips

- It's important to realize that patients have an "Opioid Debt"
  - Must be maintained on daily equivalence before ANY analgesic effect is seen with opioids used to treat acute pain
  - Opioid analgesic requirements are often higher due to increased pain sensitivity and opioid cross tolerance
- Be sure to verify current methadone doses with OTP before continuing a dose inpatient.

Peng PW, Tumber PS, Gourlay D: Can J Anaesthesia 2005
Alford DP, Compton P, Samet JH. Ann Intern Med 2006

Relapses

Substance use disorder is a chronic relapsing, remitting condition

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders: **DSM-5**. Washington, D.C: American Psychiatric Association

Naloxone

- Reverses both the clinical and toxic effects of an opioid overdose
  - Reverses respiratory depression, hypotension and sedation
  - Reverses analgesia which can also lead to precipitation of withdrawal symptoms
- No effect or harm in patients that have not taken opioids
- Quick onset ~ 3 minutes
- Short duration ~ 30-90 minutes

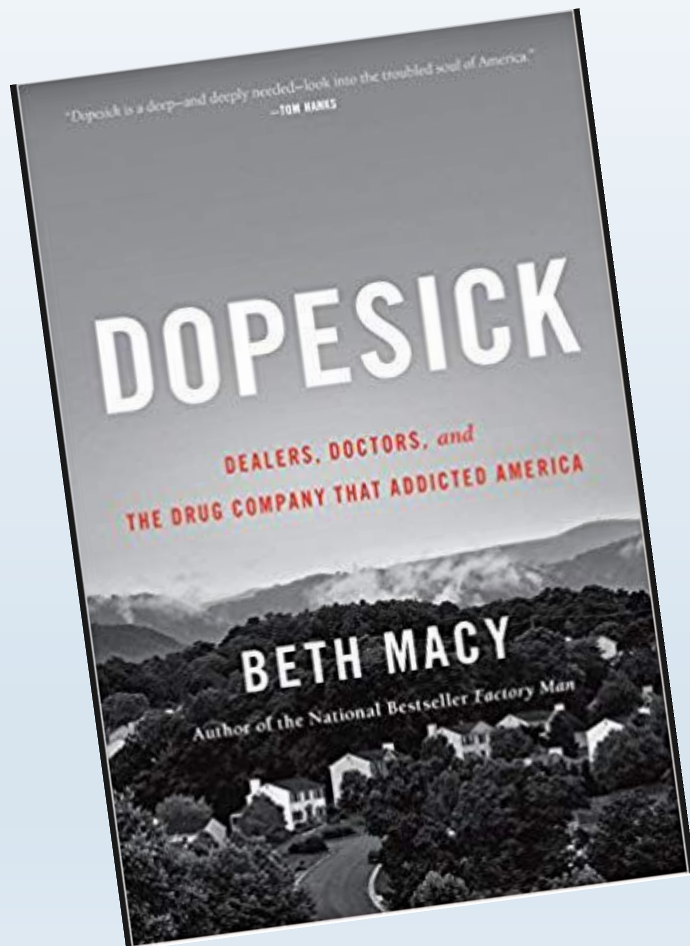
Access to Naloxone

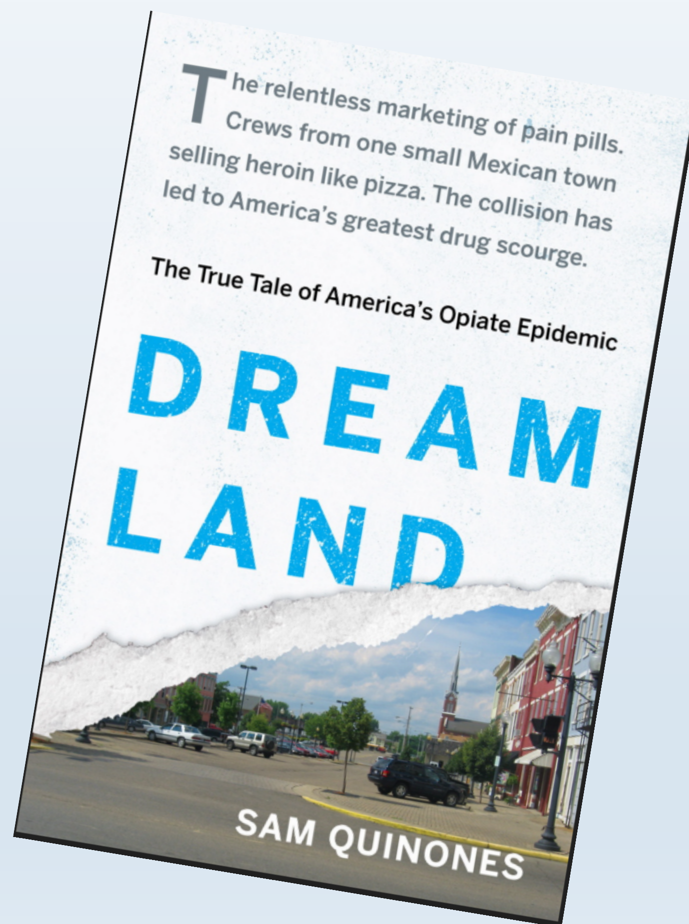
- Mississippi Code Ann 41-29-319
  - Professional Immunity
    - Physicians and Health Care Providers
      - Acting in good faith and in compliance with the standard of care, may directly or by a standing order prescribe an opioid antagonist to a person at risk of experiencing an opioid-related overdose
    - Pharmacists
      - May dispense opioid antagonists under a prescription issued directly or by a standing order
  - Layperson immunity
    - May administer an opioid antagonist that was prescribed.
  - Prescription to third parties
    - Directly, or by standing order

Learning Objectives

- Review factors that have contributed to the opioid crisis
- Describe medications currently available for Medication-Assisted Therapy (MAT) of opioid use disorder
- Differentiate myths from facts related to MAT

Thank you





References

1. CDC reportshttps://www.cdc.gov/mmwr/opioid_reports.htmlAmerican medical society
2. U.S. Department of Health and Human Services, Administration for Children and Families, Administration on Children, Youth and Families, Children's Bureau, http://www.acf.hhs.gov/programs/cb Source: https://www.acf.hhs.gov/sites/default/files/cb/afcarsreport23.pdf
3. Center for Substance Abuse Treatment. Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs. Treatment Improvement Protocol (TIP) Series 43. HHS Publication No. (SMA) 12-4214. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2005.
4. Kampman, K., & Jarvis, M. (2015). American Society of Addiction Medicine (ASAM) national practice guideline for the use of medications in the treatment of addiction involving opioid use. *Journal of addiction medicine*, *9*(5), 358.Peng PW, Tumber PS, Gourlay D: Can J Anaesthesia 2005
5. Alford DP, Compton P, Samet JH. Ann Intern Med 2006
6. https://cadca.org/comprehensive-addiction-and-recovery-act-cara
7. Mattick, R. P., Breen, C., Kimber, J., & Davoli, M. (2009). Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database of Systematic Reviews, 8*(3), CD002209.
8. Connock, M., Juarez-Garcia, A., Jowett, S., Frew, E., Liu, Z., Taylor, R. J., … Taylor, R. S. (2007). Methadone and buprenorphine for the management of opioid dependence: A systematic review and economic evaluation. In: NIHR Health Technology Assessment programme: Executive Summaries. Southhampton, UK: *NIH Journals Library*. Mattick, R. P., Ali, R., White, J. M., O'Brien, S., Wolk, S., & Danz, C. (2003).
9. Buprenorphine versus methadone maintenance therapy: A randomized double-blind trial with 405 opioid-dependent patients. *Addiction*, 98
10. Turner, C. C., Fogger, S. A., & Frazier, S. L. (2018). Opioid Use Disorder: Challenges During Acute Hospitalization. *The Journal for Nurse Practitioners*, *14*(2), 61-67. https://www.npjournal.org/article/S1555-4155(17)30979-0/fulltext#sec2
11. Connery, H. S. (2015). Medication-assisted treatment of opioid use disorder: review of the evidence and future directions. *Harvard review of psychiatry*, *23*(2), 63-75.
12. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. JAMA 2016;315:1624–45. CrossRef PubMed
13. American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders: **DSM-5**. Washington, D.C: American Psychiatric Association
14. Mississippi Code Ann 41-29-319