

# THE DISEASE OF OPIOID ADDICTION

*PHYSIOLOGY, ETIOLOGY,  
AND TREATMENT*

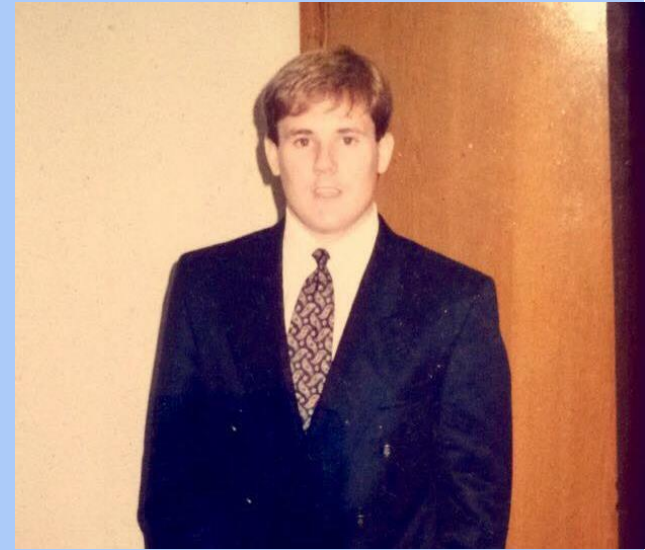
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# OBJECTIVES

- To detail the brain abnormalities and functional differences seen within individuals who suffer from addiction
- To identify several etiologies, predispositions, contributing factors, and risk factors for the development of Opioid Use Disorder
- To explore trends between opioid prescribing rates and addiction rates
- To introduce the basic treatment modalities as they pertain to Opioid Use Disorder, including their indications for treatment and ways in which to implement this into practice

# MY STORY



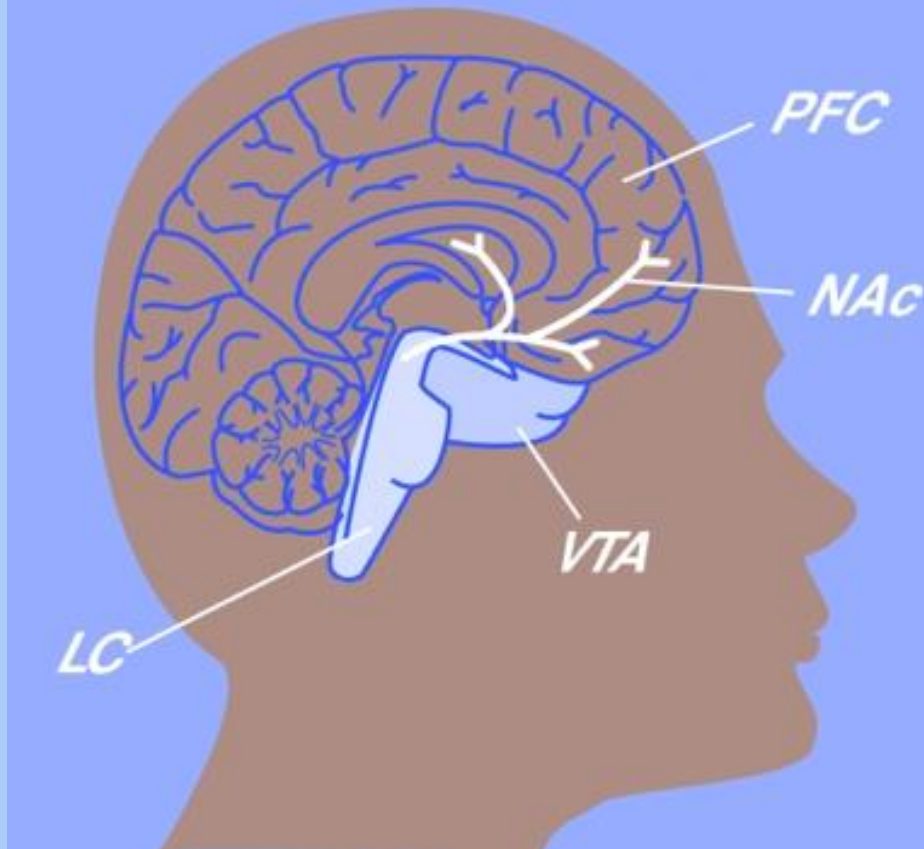
# OHIO'S OPIOID EPIDEMIC

- 1 MILLION YEARS OF LIFE LOST (YLL) in Ohio due to drug overdose from 2009-2018\*\*\*\*\*
- 2017 number of opioid overdose deaths in
  - **Ohio**: 4,293 (population 11 million)
  - **California**: 2,199 (population 38 million)
  - **Texas**: 1,458 (population 27 million)
- In 2013, these 3 states were close to being equal in deaths (1,630, 1,948, 1,053 respectively)... What changed?

# HOW DID WE GET HERE?

- Opioid prescribing increased by nearly 900% between 1997-2010
- 2010 - Average number of opioid pills per script in Ohio: 63.43
  - Average MED: 53
- 2018 - Average number of opioid pills per script in Ohio 63.43
  - Average MED: 39
- Trending downwards, but far from pre-epidemic figures (still about 3x higher than it was before epidemic began)
- 3 out of 4 heroin users started with prescription opioids...
  - Prescription opioids are how we got here!

# PHYSIOLOGY OF ADDICTION



# PHYSIOLOGY

## Midbrain

- Ventral Tegmental Area (VTA)
  - Many functions, but primary responsible for control dopamine release/inhibition throughout the brain

## Forebrain

- Nucleus Accumbens (NAC)
  - Classically referred to as the “reward center”

## Pons

- Locus Coeruleus (LC)
  - Responsible for control of norepinephrine release/inhibition throughout the brain
    - (*wakefulness/energy, BP, breathing*)

## Frontal Lobe

- Prefrontal Cortex (PFC)
  - Socially learned behaviors
    - Safe vs unsafe
    - Right vs wrong
  - Provides feedback to the VTA and NAc in attempts to control our impulse for rewards

# PHYSIOLOGY

- Opioids bind to mu receptors in the midbrain, activating the mesolimbic reward system (VTA → NAc ← PFC)
- When the VTA is activated by an opioid, this prompts the release of dopamine into the NAc, which then drives our body to repeat the behavior because dopamine is rewarding in nature
  - The amount of dopamine and the duration of time in which this dopamine is released into NAC is up to 100x stronger and longer than normal salient factors which act upon it (water, food, sleep, sex, etc)



# REWARD CENTER SURVIVAL HIERARCHY

## ■ Pre-addiction hierarchy

- Water
- Food
- Sex
- Sleep

## ■ Addiction hierarchy

### ■ Opioids

- Water
- Food
- Sex
- Sleep

# PHYSIOLOGY

- Normally, the PFC would provide feedback to our VTA to take into consideration our socially learned behaviors regarding what is safe vs unsafe, right vs wrong, in attempts to limit this excessive amount of dopamine, but this is diminished in those with addiction as seen on brain imaging
  - So in essence, individuals with addiction have an inactive frontal lobe in combination with a hyperactive reward center... a recipe for disaster

# PHYSIOLOGY - WITHDRAWAL

- Opioids also act on the LC by suppress norepinephrine (NE) coming from this area. NE is naturally activating, so if this is suppressed, the result is sedation, hypoventilation, bradykinesia, bradycardia, and hypopnea.
- In response to this, the LC up regulates and spits out more activating NE to overcome to the sedative properties of the opioids.
  - And when the patient doesn't have opioids in their system, this results in excessive NE, resulting in the classic withdrawal symptoms of jitters, anxiety, muscle cramping, diarrhea
    - ...and thus increases the drive to continue using over and over again

# ETIOLOGIES

## Biopsychosocial

- **Genetics**
  - Accounts for about 40-60% of a patient's vulnerability to develop addiction
    - PSD-95
    - DARPP-32
    - Among many others...
- **Comorbid psychological disorders**
  - Depression
  - Anxiety
  - ADHD (ESPECIALLY COMBINED TYPE\*\*\*)
    - think untreated impulsivity = high likelihood to impulsively use
- **Social factors**
  - race, poverty, peer pressure
  - past trauma, divorce, parenting styles

# TREATMENTS – AGONIST

## Methadone (Schedule II)

- Longest acting agonist in existence
- Watch prolonged QT in doses over 300mg/day
- MANY drug-drug interactions d/t P450 (primarily 3A4) system
- Increased risk of overdose compared with bupe
- Assoc. with 70% reduction in mortality rates compared to untreated heroin users – can't argue that!
- Watch respiratory depression with other sedatives such as alcohol, benzodiazepines, hypnotics, etc.
- First line choice for tx during pregnancy, and breastfeeding should be encouraged
- Only permitted in OTP and hospital inpatient settings

# TREATMENTS – PARTIAL AGONIST

## Buprenorphine (Schedule III)

- Multiple forms of bupe-only
  - **Butrans** – weekly patch, also comes in generic
  - **Buprenex** – IM/IV injection, comes in generic
  - **Sublocade** – 1 month subQ pre-filled syringe injection
  - **Probuphine** – 6 month subQ implant
  - **Generic sublingual tablet**
- Bupe + naloxone
  - *Bunavail - buccal film*
  - *Suboxone – sublingual film*
  - *Zubsolv – sublingual tablet*
- At lower doses acts like methadone, at higher doses (40+mg per day) acts like naltrexone
- Daily formulations only to be given to highly motivated patients with significant support systems

Learn more about becoming certified and registered to prescribe at  
[www.Buprenorphine.samhsa.gov](http://www.Buprenorphine.samhsa.gov)

# TREATMENT - AGONISTS

- Overall, bupe is recommended over methadone due to safety profile
- Although patients on agonist therapy are physically dependent upon the medications, they typically don't have the pattern and severity of problematic behaviors associated with addiction to heroin or prescription opioids
- After stability has been achieved and maintained, patients can taper off very slowly (months to years) without replacement therapy (as long as psychosocial support is present and no other major concerns exist)
- In an ideal situation, patient is stabilized on agonist therapy, tapered, and transitioned to antagonist therapy long-term

# TREATMENTS – MAINTENANCE

## Opioid Antagonists

### ■ Naltrexone

- Oral and LAI (Vivitrol)
- Watch liver damage, although this is very rare (seen in supra-therapeutic doses), however remember many of these patients have untreated hepatitis\*\*
- Should not be used before medically supervised withdrawal to avoid precipitation of withdrawal
- Begin 3-6 days after last opioid (if short-acting), or 7-10 days after last opioid (if longer acting – bupe or methadone)
- Can use NALOXONE challenge test to confirm absence of opioid agonists – administer drug parentally up to 0.8mg, observe vitals x 1 hour and if symptoms present or vitals change, postpone naltrexone x 24 hours

**\*\*For patients that can tolerate and achieve complete withdrawal, this should be first line treatment\*\***



# NALTREXONE SIDE EFFECTS

>10%:

Cardiovascular: Syncope (13%)

Central nervous system: Headache (3% to 25%), insomnia (3% to 14%), dizziness (4% to 13%), anxiety (2% to 12%), decreased energy (>10%), nervousness (4% to >10%)

Gastrointestinal: Nausea (10% to 33%), vomiting (3% to 14%), decreased appetite (14%), diarrhea (13%), abdominal pain (11%), abdominal cramps

Hepatic: Increased serum ALT (13%)

Local: Injection site reaction ( $\leq$ 69%; includes bruise, induration, nodules, pain, pruritus, swelling, tenderness)

Neuromuscular & skeletal: Increased creatine phosphokinase (11% to 39%), arthralgia (12%), myalgia (>10%)

# NALTREXONE SIDE EFFECTS

Cardiovascular: Hypertension (5%)

Central nervous system: Suicidal ideation ( $\leq 10\%$ ), delayed ejaculation ( $< 10\%$ ), depression (8%), drowsiness (2% to 4%), fatigue (4%), chills, depressed mood, increased energy, irritability

Dermatologic: Skin rash (6% to 10%)

Endocrine & metabolic: Increased gamma-glutamyl transferase (7%), increased thirst, polydipsia

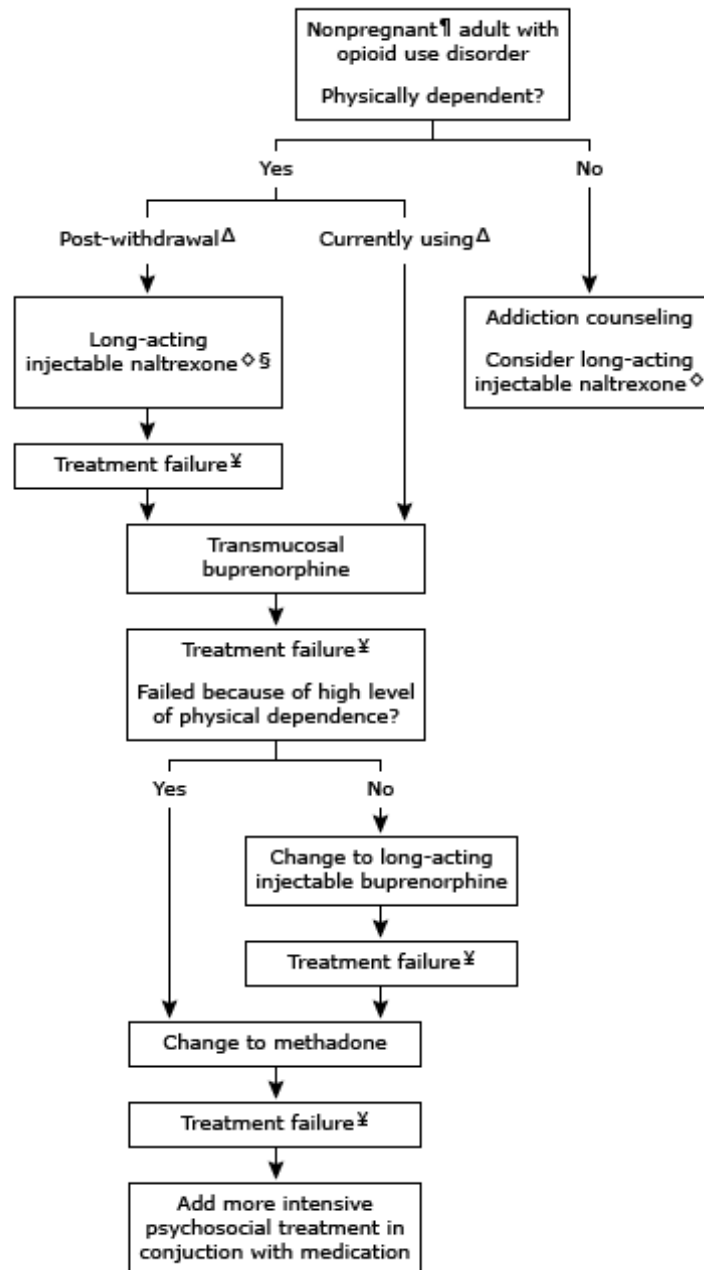
Gastrointestinal: Xerostomia (5%), toothache (4%), constipation

Genitourinary: Impotence ( $< 10\%$ )

Hepatic: Increased serum AST (2% to 10%)

Infection: Influenza (5%)

# Approach to medication-assisted treatment for opioid use disorder\*



# KEY POINTS

- Language matters
  - Stigma is real
- Our brains are not operating at the same capacity, remember this is a brain disease!
- Show compassion and most of all, be educated. That is our duty in the medical profession.
  - Be open to treating OUD, it CAN and WILL save lives
- If we played a part in creating this issue, the least we can do is to play our part in fixing the damage that continues to occur on a daily basis

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