# Opioid Use Disorder

## Concepts in Medical Management

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# During this part of the discussion:

- Concepts defining substance use disorders
- Types of opioid medications and the pharmacologic properties that define them
- Medications used to treat opioid use disorder

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# WHY Do We Use Medication??

- During withdrawal and protracted abstinence, patients have increased sensitivity to pain, a frequent trigger of relapse.
- Overexpression of transcription factors which increase sensitivity to rewarding effects of drugs which remain for weeks-months after drug use
- Opioid receptor desensitization & internalization
- Because, for most people, abstinence-based recovery does not work for OUDs with failure rates 80-90% or more.  Multiple factors.

- **Increased stress response activation**
- **Decreased reward system activation**

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# American Society of Addiction Medicine Definition of Addiction

Addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry.

Dysfunction in these circuits leas to characteristic biological, psychological, social and spiritual manifestations.

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# ASAM Definition of Addiction (cont'd)

This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors. Addiction is characterized by inability to consistently abstain, impairment in behavioral ***control,*** **craving**, diminished recognition of significant problems with one's behaviors and interpersonal relationships and a dysfunctional emotional response. Like other chronic diseases, addition often *involves* ***cycles of relapse and remission***. Without treatment and engagement in recovery activities addiction is progressive and can result in disability or premature death.

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# DSM V Definition of Substance Use Disorders

- Unsuccessful efforts to cut down
- Activities given up because of use
- Failure to fulfill major role obligations
- Recurrent use in hazardous situations
- Withdrawal symptoms*
- Tolerance
- More use than intended
- Recurrent use resulting in physically hazardous situations
- Craving for the substance
- Significant time spent acquiring substance
- Continued use despite negative consequences
- Continued use despite consistent social/personal problems

*Severity measured by # of symptoms:
2-3 Mild. 4-6 Moderate. 7-11 Severe.

# Euphoria Producing Drugs

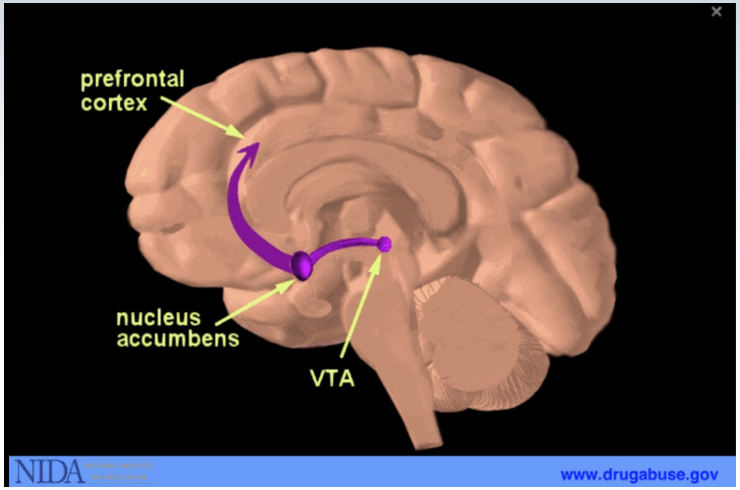
EPDs include: opioids, stimulants, sedative hypnotics, cannabinoids, phencyclidine (PCP, “angel dust”)

These have very different primary effects.

ALL produce an acute surge of dopamine in both the midbrain and forebrain.

Dopamine surges mediate addictive disease, activating the complex behavioral surge of addictive behaviors.

# Mesolimbic Pathway




VTA projects to all cortical structures and structures of the limbic system. The limbic system controls basic emotions (fear, pleasure, anger) and drives (hunger, sex, dominance).

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# Opioids/Opiates

OPIOIDS: refers to all compounds, natural and synthetic, functionally related to opium derived from poppies (and our endogenous neuropeptides).

OPIATES: refers to naturally occurring opioids.

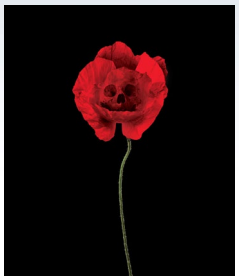

Photo Illustration:
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# Naturally Occurring Opioids (Opiates)

- Morphine from the opium poppy
- Codeine, also found in opium, can be made synthetically

# Semi-Synthetic Opioids

- Heroin, synthesized from morphine
- Hydromorphone
- Hydrocodone
- Oxycodone
- Buprenorphine

# Synthetic Opioids

- Fentanyl
- Methadone
- Tramadol
- Dextropropoxyphene
- Meperidine

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# The Family of Opioid Receptors

***Mu*** Mediates analgesia, euphoria, respiratory depression. Natural agonist: **beta-endorphin**

***Delta*** Analgesia in synergy with mu, antidepressant. Natural agonist: **dynorphin.**

***Kappa*** Analgesia, dysphoria, hallucinations, mood. Natural agonist: **metenkephalin**

***NOP*** Nociceptin opioid peptide receptor (NOP), also known as the nociceptin/orphanin FQ receptor (N/OFQ) receptor, previously called the opioid receptor-like receptor (ORL-1). Related to anxiety, stress.

Well known ***mu*** *r*eceptor polymorphism

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# FDA Approved Medications for the Treatment of OUD

- Methadone
- Naltrexone (Vivitrol®)
- Buprenorphine/Naloxone (Suboxone®)

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# Opioid Agonist Spectrum

- Full Agonist — Methadone
- Partial Agonist — Buprenorphine
- Antagonist — Naltrexone

  Binds to *mu* receptor; does not produce biologic effect

- Inverse Agonist — Naloxone

  Reverses agonist effects and blocks effects of agonist

# What Determines Opioid Effects?

- Receptor Affinity  how tightly drug binds, resists displacement
- Dissociation  how fast drug leaves the receptor
- Intrinsic Activity  how intensely drug stimulates receptor

# Methadone

- Developed in 1960s. Licensed in 1970s.
- Largest, oldest evidence-based treatment of OUD
- WHO: an essential medication
- Longer duration of treatment = improved outcomes. Years!

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# Methadone Maintenance Treatment

- Many medications potentiate/inhibit serum levels via hepatic metabolism including anti-retrovirals, TB drugs
- Long half live with variable rates of individual metabolism
- Affected by chronic diseases
- Methadone itself not associated with liver damage.  Many patients have hepatitis B, C
- MUST BE PRESCRIBED BY A FEDERALLY LICENSED DISPENSARY ONLY FOR OUD!!!!

# Naltrexone XR-NTX

- An opioid receptor antagonist.  FDA approved 2010.
- Oral form non-superior to placebo or no medication.
- Non-adherence limits its use.
- Longer acting form (Vivitrol®) reduced illicit opioid use.
- Retains patients in treatment longer than placebo/nothing.
- Increased time to relapse.

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# Buprenorphine

- A semi-synthetic derivative of thebaine (an opium alkaloid)
- First made in 1969
- Highly lipid soluble
- High sublingual availability (>60%). Poor oral availability
- Excreted in bile
- $T_{1/2}$ = 20-73 hours
- 30:1 MME

# Buprenorphine

- ***Mu*** partial agonist
- ***Kappa*** antagonist

- Very high receptor affinity (vs. tramadol)

# Buprenorphine

- High receptor affinity means that buprenorphine is not easily displaced from the *mu* receptor

- If you precipitate withdrawal it will be hard to reverse

- Agonist effects are not reversible with naloxone
- Naloxone is effective if given before but not after

# Buprenorphine

## Differences from Other Opioids

- In opioid-dependent patients abusability for euphoric effects is significantly lower (altered *mu* receptor tone)
- Not entirely suitable for chemically addicted patients with a high level of dependence or for chronic pain patients on high doses of opioids
- Kappa antagonism may protect against addiction behaviors via its effect on mood.
- In opioid dependent persons, even those with high degrees of tolerance, there is a high potential for overdose death caused by combinations of buprenorphine and sedative-hypnotics (benzodiazepines, alcohol, SOMA and others)

# Final Considerations

- Medication treatment for opioid use disorder is first-line harm reduction.
- The goal is stabilization with elimination of withdrawal symptoms and drug cravings.
- This facilitates patients entering into the *real* treatment for addiction.
- Some people will never be able to stop using drugs. The best treatment may be supervised injection sites.

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# Final Considerations

- There is no addiction gene.
- Addiction is a response to pain, severe life stress, trauma.
- It is an attempt to solve a problem.
- Addiction is not treated by medication or simply stopping the behavior.
- The solution lies in trauma-informed care and relationships.

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