The Neurobiology of Addiction &
the Pharmacology of Suboxone

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Objectives
• Discuss the basic neurobiological processes leading to drug addiction
• List two medication approaches in the treatment of opioid use disorder
• Review the basic and clinical pharmacology of buprenorphine and suboxone

Disclosures:
• The speaker has no financial or other conflicts of interest to disclose

Addiction (ASAM definition)
• A primary, chronic disease of brain reward, motivation, memory and related circuitry.
Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors.

Addiction (ASAM definition)
• 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, addiction often involves cycles of relapse and remission.
• Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death.

Three “C’s” of Addiction
• Control
  – Early social / recreational use
  – Eventual loss of control
  – Cognitive distortions ("denial")
• Compulsion
  – Drug-seeking activities
  – Continued use despite adverse consequences
• Chronicity
  – Natural history of multiple relapses preceding stable recovery
  – Possible relapse after years of sobriety

Drug Addiction: A Complex Disorder

Historical
- Past experience
- Expectation
- Memory

Physiological
- Genetics
- Disease states
- Gender

Drugs

Brain Mechanisms

Behavior

Environment
- Social interactions
- Stress
- Conditioned stimuli
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It all starts in the VTA with Dopamine

Dopamine and Reward

- Behavior which stimulates the release of dopamine in the nucleus accumbens is associated with the sensation of pleasure.
- People seek out experiences which provide pleasure and reward. These natural rewards act upon the dopamine reward pathway.

Natural Rewards and DA

Why Do People Take Certain Drugs in the First Place?

To feel good
- To have novel feelings, sensations, experiences of altered states of consciousness and to share them

To feel better
- To lessen anxiety, worries, fears, depression, hopelessness

Risk Factors for Addiction

- Genetics
  - neurophysiology, receptors, transporters, etc
- Age of substance abuse (younger worse)
- Childhood trauma (emotional, violence, sexual)
- Comorbid psychiatric disorders:
  - Most prevalent
    - Mood disorders
    - Anxiety disorders
    - Personality disorders
    - Psychotic disorders

Circuits involved in Addiction

- Prefrontal cortex and the anterior cingulate gyrus provide inhibitory control and emotional regulation
- Orbitofrontal cortex is involved in decision-making and determining the expected rewards and punishments of an action
- Nucleus accumbens assesses reward and salience
- Amygdala and hippocampus involved in forming memories of the stimulus/reward relationship

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The Road to Addiction

• In the beginning, the nucleus accumbens in the ventral striatum and its functional interaction with the basolateral amygdala are responsible for developing voluntary drug-seeking behaviour.

• The NA plays an important role in dopamine-dependent reward circuits that turn motivation into action, while the BLA provides positive consolidation of drug-associated memories with environmental cues.

Neurotransmitters implicated in the Motivational Effects of Drugs of Abuse

Positive Hedonic Effects

- Dopamine
- Endorphins
- Serotonin
- GABA

Natural Reward vs. Drug-Induced Reward

Food, Sex, Excitement
Addictive Drugs

Effects of Drugs on Dopamine Release

- Amphetamine
- Cocaine
- Nicotine
- Alcohol

Time after Administration

The Road to Addiction

• Continued exposure to opioids stimulates neuroplastic changes in the striatum, with control passing to the anterior dorsolateral striatum (decision region).

• This functional shift in neural control, from habitual to compulsive drug-seeking behaviour, is greatly influenced by drug-associated Pavlovian conditioned stimuli that induce drug-cravings and even relapses after abstinence.
Repeated release of DA will continually promote new learning and Long-term potentiation - therefore consolidating drug-seeking and drug-taking behaviors more rapidly and to a greater degree than physiological rewards.

Continual activation of the pathway alters the availability of DA
Reduction and/or down-regulation in dopamine availability has a blunting effect on the natural reward circuit
Leads to neuroplastic changes at higher cortical sites

Addiction tricks the brain into believing that drugs are necessary for survival.
The drive to use becomes as powerful as the drive to find food and water.
The executive system’s longer term goals such as maintaining healthy relationships, pursuing educational or professional objectives, or maintaining one’s reputation and legal status are all overridden by the drive to use.

Neurotransmitters implicated in the Motivational Effects of Drugs of Abuse

Dopamine
Endorphins
Serotonin
GABA

Pain
Dysphoria
Anxiety
Craving

Pharmacological Options for Treatment
Medication Strategies (MAT)

- **Agonist / Partial Agonist**
  - Substitute effects of drug
  - Harm Reduction
  - Buprenorphine +/- naloxone, Methadone

- **Antagonist**
  - Block the effects of drug
  - Reduce cravings
  - Naltrexone / Vivitrol

- **Deterrent Medications (aversive)**
  - Naloxone in Suboxone

**Buprenorphine**

- Semi-synthetic opioid
- Partial agonist at Mu receptors
- Antagonist at Kappa receptors
- Less euphoria

- Produces feelings of euthymia - a general feeling of good mood, not a euphoria like with an opioid
- Suppresses cravings for opiates and prevents withdrawal symptoms when taken as prescribed orally

**Buprenorphine**

- 25 to 50 times more potent than morphine
- Poor oral absorption
- Significant 1st-Pass effect (CYP3A4)
  - Which is why sublingual route is used
- Maximal effects peak slower than morphine
  - Slow dissociation from receptor, extended duration of action, less/milder withdrawal when discontinued
- Primary side effects:
  - nausea and constipation
  - like other mu agonist opioids, but may be less severe and more self-limiting

**Suboxone**

- **Buprenorphine** – poor oral / good SL bioavailability
- **Naloxone** - limited bioavailability both PO and SL
- When taken sublingually
  - Buprenorphine will be well absorbed
  - Naloxone absorption will be minimal
- If taken intravenously
  - Naloxone becomes 100% bioavailable
  - Can attenuate effect of buprenorphine
  - Can precipitate withdrawal in opioid-dependency

- The combo product, if crushed, dissolved and injected the:
  - naloxone may cause initial withdrawal if the person is opioid physically dependent.
  - decreasing diversion and misuse
  - naloxone will block, or attenuate, the opioid agonist effect of the buprenorphine
  - therefore safer if diverted

- First therapy approved for in-office prescribing for opioid dependence under the Federal Drug Addiction Treatment Act of 2000
Overdose Risk Minimal
- Low risk of clinically significant problems
- Pre-clinical studies suggest high doses of buprenorphine should not produce respiratory depression
- No reports of respiratory depression in clinical trials
- Overdose and misuse (e.g., injecting) of buprenorphine combined with other CNS depressants result in respiratory depression and risk overdose
- In Europe
  - IV buprenorphine + high potency benzodiazepines → deaths

Who Might Abuse Suboxone?
- Can be abused
  - Risk may be greatest in new opioid abusers
- Untreated Opioid Addicts
- Treated Opioid Addicts
  - Methadone maintenance patients
  - Buprenorphine treated patients
- Buprenorphine stabilized addicts will not experience adverse effects injecting Suboxone
  - Buprenorphine has higher Mu affinity than naloxone
  - Will not have pleasurable effects either
  - Suggests low abuse liability in this population

Abuse Potential of Buprenorphine
- Euphoria in non-opioid dependent individuals
  - Abuse potential less than full opioid agonists
  - Abuse among opioid-dependent individuals is relatively low
  - Buprenorphine is weaker opioid but with higher Mu affinity which can act like narcan leading to withdrawal
- Combination product (Suboxone) theoretically less likely to be abused by IV route
- Most common use in addicts is to prevent or treat withdrawal and cravings (already in withdrawal)

Questions?

Thanks for listening . . .
Alan