The Neurobiology of Addiction
A presentation on the science of addiction, focusing on drugs of abuse and treatment

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At the time of this presentation, Elinore F. McCance-Katz, served as SAMHSA Assistant Secretary. The opinions expressed herein are the views of Dr. Andrew McLean, MD, MPH and do not reflect the official position of the Department of Health and Human Services (DHHS), SAMHSA. No official support or endorsement of DHHS, SAMHSA, for the opinions described in this document is intended or should be inferred.
Objective

- To understand the general concept of addiction as it relates to the brain
Substance-Related Disorders

• Substance Use Disorders: Clusters of cognitive, behavioral and physiological symptoms indicating that the individual continues using the substance despite significant substance-related problems.

• Substance-Induced Disorders: Intoxication, withdrawal, and other substance/medication-induced mental disorders.
Specifiers:

• Severity:
  • Mild (i.e., presence of 2-3 symptoms)
  • Moderate (i.e., presence of 4-5 symptoms)
  • Severe (i.e., presence of 6 or more symptoms)

• Remission:
  • Early (no criteria for > 3 months, < 12 months)
  • Sustained (12 months or more without criteria)
  • On maintenance therapy

• “Craving” or “urge to use” do not impact remission criteria
Classification of Mental Disorders History

- Initially statistical - 1840 census “idiocy/insanity”
- By 1880, seven categories of mental illness, including melancholia, monomania, paresis, dementia, epilepsy and dipsomania
- APA - diagnosis of severe illness
- U.S. Army - inclusion of “outpatient” illnesses
- World Health Organization - ICD (International Classification of Diseases)
- APA in 1952 established 1st DSM, a variant of ICD-6
Paradigms

• Disease

• Emotional or Moral Weakness

• Spiritual problem
Substance Use Disorders

- Brain Based Disorders
- Genetic and Environmental factors
Substance Use Disorders Continuum

- Withdrawal Management
- Treatment/Rehabilitation
- Maintenance

Relapse
The Onset of Addiction

• Contagious vs Sticky

• Genetics

• Chippers vs Addicts

1Malcom Gladwell’s “The Tipping Point”
Risks

- **Environmental triggers/associations:**
  - Stress
  - Trauma
  - Early exposure to drugs
ACES (adverse childhood experiences) and substance use

- If > 1 ACE:
  - Likelihood of having a drug problem = 56%
  - Likelihood of being addicted to illicit drugs = 63%
  - Likelihood of ever using parenteral drugs = 64%

- And, with each additional ACE, increase risk by 30-40%
Goals

• For most, rehabilitation:
  Stop drug use, avoid relapse, function in a healthy way without the drug. Abstinence.

• For some, harm reduction without total abstinence.
Comorbidity is the rule
<table>
<thead>
<tr>
<th>Neurotransmitters</th>
<th>Gut Hormones</th>
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<tbody>
<tr>
<td><strong>Amines</strong></td>
<td><strong>Opioid Peptides</strong></td>
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<tr>
<td>Serotonin (5HT)</td>
<td>Dynorphin</td>
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<td>Dopamine (DA)</td>
<td>β-Endorphin</td>
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<td>Norepinephrine (NE)</td>
<td>Met-enkephalin</td>
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<td>Epinephrine (E)</td>
<td>Leu-enkephalin</td>
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<tr>
<td>Acetylcholine (ACh)</td>
<td>Kyotorphin</td>
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<tr>
<td><strong>Pituitary Peptides</strong></td>
<td><strong>Miscellaneous Peptides</strong></td>
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<tr>
<td>Corticotropin (ACTH)</td>
<td>Bombesin</td>
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<td>Growth hormone (GH)</td>
<td>Bradykinin</td>
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<td>Lipotropin</td>
<td>Carnosine</td>
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<td>α-Melanocyte-stimulating hormone (α-MSH)</td>
<td>Neuropeptide Y</td>
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<td>Oxytocin</td>
<td>Neurotensin</td>
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<td>Vasopressin</td>
<td>Prolactin</td>
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<td><strong>Circulating Hormones</strong></td>
<td>Substance K</td>
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<td>Angiotensin</td>
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<td>Calcitonin</td>
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<td>Glucagon</td>
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<td>Insulin</td>
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<td><strong>Hypothalamic-Releasing Hormones</strong></td>
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<tr>
<td>Corticotropin-releasing factor (CRF)</td>
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<td>Luteinizing-hormone-releasing hormone (LHRH)</td>
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<td>Somatostatin</td>
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<td>Thyrotropin-releasing hormone (TRH)</td>
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Table 1-1. Neurotransmitters in brain
Mesolimbic Pathway

- Alcohol
  - GABA receptor
  - NMDA receptor
- Cocaine
  - Monoamine transporters
- Morphine
  - Opioid receptors

Mesolimbic Dopamine System
(Ventral tegmental area, Nucleus accumbens, medial prefrontal cortex)
Salience!

Dopamine

- Attention
- Reward
- Motivation
- Pleasure
The Nerve Cell Unit (dopamine example)
Pick your parents carefully…
Specific categories of drugs

Some gene targets

- Linkage QTLs
- GWAS QTLs
- Expression arrays

Gene targets in addiction
- ADH1B
- ALDH2
- DRD4
- GABA_A
- CHRNA5
- SLC6A4
- COMT
- MAOA...

Functional studies
- Putative functional variants
- Epigenetic patterning
- In vitro mRNA
- In vivo mRNA
- Peptide/ enzyme
- Brain imaging
- Neuropsychological

Functional loci

Mus musculus

Homo sapiens

Drosophila melanogaster

Bevilacqua L, Goldman D. Clin Pharmacol Ther. 2009 Apr;85(4) 359-361
Some neurotransmitters inhibit, some excite, some actually do both. Some act quickly, some act more slowly.

In addition to the number of actual neurotransmitters, there are many types of neurotransmitter transporters...
Transmission

- **Electrical**-
  - Usually within the cell

- **Chemical**-
  - Usually between cells

Can be inhibitory

Can be excitatory
The synapse

1. Incoming electrical signal
2. Neurotransmitters
3. Vesicles
4. Synaptic gap
5. Ion gate
6. Chlorine ion
7. Sodium ion
8. Transmitted signal
9. Reuptake port
10. Auto receptor
Dopamine

- Reward
- Motivation
- Control

Some individuals with substance use disorders have fewer D2 (dopamine) receptors in many brain regions. Post use of some drugs can take months for the brain to return to baseline.
• Normal rewards (food, sex, etc...) might be like a whisper

• Drug rewards might be like a shout. And, some are louder than others.

From NIH, and the Surgeon General’s Report
After taking drugs for a while, the brain will try to compensate/protect itself, reducing the number of receptors, (i.e., “it’s too much…."

Often, the ability to experience pleasure from normal rewards (as well as drugs) is reduced. Thus, depending on the drug, the individual may feel more flat, irritable, and find themselves needing more drug.
Simplistic analogy

• “Accelerator”: priming, drug cues, craving, and stress

• Brake dysfunction: Inhibitory dyscontrol
A) Schematic, sagittal view of a brain depicting 4 circuits that are postulated to have key interdependent and overlapping roles in addiction: (1) reward prediction and the core substrates of pleasure (red) located in the nucleus accumbens and ventral pallidum; (2) memory and learning, and the main substrate of conditioning (purple), located in the amygdala and hippocampus; (3) motivation, drive, and salience evaluation (green) located in the orbitofrontal cortex; and (4) cognitive control (blue), in charge of restraining cravings, located in the prefrontal cortex, and anterior cingulate gyrus. (B) Hypothetical model of addiction as the result of impaired information processing within the reward network. Compared with the nonaddicted state (left), the salience value of a drug (red), and its associated cues (purple), is enhanced in the addicted state (right), whereas the strength of inhibitory control is weakened (blue), setting the stage for an unrestrained motivation (green) resulting in compulsive drug taking without regard to potentially catastrophic consequences.

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Euphoric Recall

- Both the visceral and cognitive response to triggers

- Some describe it as overvaluing previous “positives” of using and minimizing the “negative.”
Withdrawal

- More or less, opposite of intoxication symptoms.

- With alcohol, also risk of convulsions, delirium tremens.
• **Depressants** (alcohol, benzodiazepines, barbiturates, etc...)

• **Opioids** (prescription pain meds, heroin, codeine, methadone, buprenorphine...)

• **Stimulants** (amphetamines, cocaine, methylphenidate, as well as caffeine, nicotine, etc...)

• **Cannabinols**

• **New Psychoactive Substances (Synthetics)**

• **Hallucinogens**
Depressants tend to:
Facilitate GABA_A receptor function  
(GABA is primary inhibitory neurotransmitter)
And
Inhibit NMDA glutamate receptor function  
(Glutamate is primary excitatory neurotransmitter)

Stimulants tend to:
Do the opposite.
Depressants
(alcohol, benzodiazepines, barbiturates, etc...)

- High: Silly, laid back. Occasionally disinhibition
- Decrease in anxiety
- Decrease in blood pressure, temperature. At high doses, respiratory depression.
- Sedation, dysarthria, ataxia
- Muscle relaxation
- Overdose: Dangerous
Stimulants

• **INTAKE**

• Oral
• Snorting
• Smoking
• Injection
Stimulants

- **Cocaine, amphetamines, methamphetamine, etc...**

- **Amphetamines primarily act pre-synaptically to enhance availability of dopamine.**

- **Cocaine inhibits transporter (re-uptake).**
Stimulants

- **Intoxication**: “rush”, euphoria, decreased sleep, appetite, increased stereotypic behavior. Paranoia may occur. Increased pulse, BP, temp. Risk of stroke.

- **Withdrawal**: opposite symptoms - Crash. Peaks in couple of days, over by day five. But lingering symptoms such as moodiness, cognitive difficulty. High relapse risk. Cues, euphoric recall.
• **Telescoping/Compression**

• **Physical**

• **Mental**

• **Social**
Interesting finding: people with damage to the insula have significant difficulty quitting smoking...

Mechanism of Action of Nicotine in the Central Nervous System

- Nicotine binds predominantly to nicotinic acetylcholine (nACh) receptors in the CNS; the primary is the α4β2 nicotinic receptor in the Ventral Tegmental Area (VTA).
- After nicotine binds to the α4β2 nicotinic receptor in the VTA, it results in a release of dopamine in the Nucleus Accumbens (nAcc) which is believed to be linked to reward.
Substances for Which

• We have MAT
  • Tobacco
  • Alcohol
  • Opioids

We don’t have MAT

• Marijuana
• Cocaine
• Methamphetamine
• Synthetics
• Hallucinogens
• Inhalants
Most successful with a smoking cessation program.

- **Nicotine replacement**
- **Gum, nasal spray, patch, lozenge, etc…**
  - *Bupropion* (Zyban/Wellbutrin)
  - *Varenicline* (Chantix)
- **Many other non-pharmacologic treatments including acupuncture, hypnosis, etc…**
- **Vaping is too early to tell**
Caffeine: A Socially acceptable psychoactive drug... (and the most abused substance in the world...)

- Avg. US consumption 300mg per day (2-4 cups)

- Consumer Reports recommends safe limits as:
  - 400mg per day for health adults
  - 200mg per day for pregnant women*
  - 45-85mg per day for children, depending on weight.

- Over 400mg per day linked with insomnia, irritability, tachycardia, migraine headache, restlessness, frequent urination, G.I. upset, tremors. (Mayo Clinic)
What are opioids?

- **Opiates** - drugs derived from opium.

- **Opioids** - term previously used to describe synthetic opiates.

- *Now it is common to refer to all as “opioids.”*
Opioids

Rush of euphoria, tranquility, then drowsiness, mood changes, mental clouding, motor slowing.

Constipation

Overdose: respiratory collapse

Coma

(potent effects on brainstem and spinal cord)
How is opioid misuse a different type of problem than other substances?

• The good news- withdrawal is usually not potentially life-threatening, as opposed to withdrawal from alcohol, some CNS depressants

• Depending on supply and demand, some individuals cycle from prescription misuse to street use.

• Bad news- for unknown quantities (particularly with heroin, “counterfeit” pills, and synthetic analogues/fentanyl) one time use can result in death. In other words, a person might not even have time to become “addicted.”
Marijuana refers to the dried leaves, flowers, stems, and seeds from the *Cannabis sativa* or *Cannabis indica* plant.

- There are hundreds of compounds in marijuana.
Marijuana

- Can have both stimulant and sedative properties.
- Antiemetic properties*
- Anticonvulsant effects
- Muscle-relaxing effects
- Reduction of intraocular pressure
THERAPEUTIC EFFECTS
In adults with chemotherapy-induced nausea and vomiting, oral cannabinoids are effective antiemetics.

In adults with chronic pain, patients who were treated with cannabis or cannabinoids are more likely to experience a clinically significant reduction in pain symptoms.

In adults with multiple sclerosis (MS)-related spasticity, short-term use of oral cannabinoids improves patient-reported spasticity symptoms.

For these conditions, the effects of cannabinoids are modest; for all other conditions evaluated, there is inadequate information to assess their effects.

CANCER
The evidence suggests that smoking cannabis does not increase the risk for certain cancers (i.e., lung, head, and neck) in adults.

There is modest evidence that cannabis use is associated with one subtype of testicular cancer.

There is minimal evidence that parental cannabis use during pregnancy is associated with greater cancer risk in offspring.

CARDIOMETABOLIC RISK
The evidence is unclear as to whether and how cannabis use is associated with heart attack, stroke, and diabetes.

RESPIRATORY DISEASE
Smoking cannabis on a regular basis is associated with chronic cough and phlegm production.

Quitting cannabis smoking is likely to reduce chronic cough and phlegm production.

It is unclear whether cannabis use is associated with COPD, asthma, or worsened lung function.

The National Academies of SCIENCES · ENGINEERING · MEDICINE
Little is known about the safety of individual compounds. Serious adverse effects are rare with cannabis or its constituents.

Marijuana has low to moderate dependence potential; the active dose is very far below the lethal dose (Gable et al 2006).
THC vs CBD

Tetrahydrocannabinol

Cannabidiol

Image from FarmaPDX.com
• THC
  • Dronabinol as Marinol
  • Approved for AIDS associated anorexia or treatment-resistant nausea/vomiting secondary to cancer chemotherapy
  • Most psychoactive substance in marijuana

• CBD
  • FDA Approved as Epidoliex for:
    • Lennox-Gastaut Syndrome and
    • Dravet Syndrome
CBD

• Is it the best thing ever?

• Is it psychoactive or is it not?

• What are the side effects?
Why do people use CBD?


**FIG. 1.**

Number of medical conditions for which respondents reported using CBD, by medical condition ($n=3963$). CBD, cannabidiol; COPD, chronic obstructive pulmonary disease; PTSD, post-traumatic stress disorder.

**FIG. 3.**

Number of medical conditions for which respondents report CBD treating “Very Well by Itself” or “Moderately Well by Itself,” by medical condition ($n=2557$).
Absorption and bio-availability

- **Smoking or vaporizing** allows for pulmonary first-pass metabolism with direct systemic blood stream absorption across lung lining. THC bio-availability ~ 30%

- Similarly, **sublingual** (i.e., use of oils, etc...) absorption also avoids first-pass metabolism, with slightly less rapid absorption than above. Bio-availability ~20%?

- **Edible use**-absorbed via intestinal mucosa and transported to the liver and metabolized prior to reaching other organs, such as the brain. THC bio-availability ~10%

- Only about 1% of administered TCH dose reaches the brain.

- **However-** THC variability in marijuana plants can range from 0.3-30% or higher
Areas of the brain where THC acts

- movement
- sensations
- vision
- judgment
- reward
- memory
- coordination
CB1 receptors
mainly localized in the brain
(hippocampus, cerebellum and cerebrum)

CB2 receptors
mainly situated in the periphery
(spleen, tonsil and immune cells)
Some Psychoactive effects of THC

Acute effects: Usually temporary and reversible, and do not present a risk of harm (outside of risk of activities when intoxicated).

Pleasant: Euphoria and relaxation.

Sleepiness

Unpleasant: Anxiety Paranoia/Psychotic symptoms, depending on genetic and vulnerability characteristics
A number of studies have linked THC use with a higher incidence of schizophrenia.

However, Proal and DeLisi’s Harvard study, indicated a genetic predisposition is necessary.

As such, use of marijuana in teens and young adults with such risk may initiate onset.
Study of Canadian medical marijuana users

- **Subjective acute reduction in anxiety, depression and stress**

- **Subjective increase in depression over time with chronic use**

Cannabis Withdrawal Syndrome
Bonnet and Preuss, *Subst Abuse Rehabil.* 2017; 8: 9–37

O= none, 1=mild, 2=moderate, 3=heavy
New Psychoactive Substances (NPS)

• Synthetic Cannabinoids ("K2," "Spice"). Binds to CB1 receptors at five times the affinity of THC.

• JW Huffman, chemist and research developer: Likened using it to playing “Russian Roulette,” and that those who try it “must be idiots…”

• Synthetic Cathinones ("bath salts") such as MDPV—synthetic derivative of khat. Excited delirium not uncommon.
Hallucinogens

1) Serotonin-like (indole alkylamines)
LSD, psilocybin, etc...

2) Resemble norepinephrine/dopamine
(phenylalkylamines)
Mescaline

Ecstasy “Molly,” methylenedioxymethamphetamine (NDMA) somewhat similar.
Unfortunately often adulterated
Hallucinogens

- Visual illusions, “trails” or “tracers”
- Expansive, “religious” sense
- “Trading senses” (synesthesia)
- Change in sense of time
- Depersonalization/derealization
- Increased pulse, BP, temp
- Can approach delirium
Hallucinogens

• Much research occurring in palliative/hospice care as well as for psychiatric conditions.

• As with THC, still Schedule 1.
Dextromethorphan (DXM/Skittles)

- Often abused by adolescents

- Abuse-euphoria, perceptual changes, altered time perception, paranoia—more serious, seizures, arrhythmias, rare sudden death.

- Withdrawal- insomnia, dysphoria

- Metabolite dextrorphan binds to
Therapies/Models for Substance Use Disorders

- Group-12 step and non-12 step
- Manual based-therapies
- CBT
- Motivational Enhancement Therapy
- Family Behavior Therapies
- Community Reinforcement Approach/vouchers
- Psychosocial
- Biofeedback
- Peer supports

- MAT (Medication Assisted Treatment)

- Harm Reduction
• **Disulfiram** (Antabuse) Aversive therapy.
  • 1500mg/week

• **Naltrexone** (Revia) 50mg/day
• *(Vivitrol)* - monthly injection 380mg – issue of pain meds*

• **Acamprosate** (Campral) (2) 333mg tabs T.I.D

• **Others**
Opioids (Heroin, Prescription Drugs, etc…)

- **Replacement Therapies:**
  - **Methadone:** Special outpatient treatment center
  - **Buprenorphine:** (partial agonist)/naloxone (antagonist) =
    - Indicated for maintenance treatment in opioid use disorder. Office-based
    - 1) Induction 2) Stabilization 3) Maintenance

- **Opiate Blockade:**
  - Naltrexone (Revia/Depade) and monthly injection Vivitrol
No longer use the term “Detox”
Use “Withdrawal Management.” We have “social,” we have “ambulatory,” we have “medically monitored,” we have “medically managed,” etc…

• Alcohol
  • Benzodiazepines
  • Anti-convulsants

 opioid
  • Buprenorphine/other*
  • δ-2 agonist (clonidine/lofexidine)
What about genetic testing?

• Not there yet.
We discussed a number of issues related to the neurobiology of addiction, including:

- General concepts regarding mechanism of action
- Specific drugs
- Intoxication and withdrawal
- Ongoing research.

Thoughts, Comments, Questions?