

The Neurobiology of Addiction and Pharmacological Concepts

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### Facts About Addiction

- Addiction affects 22 million Americans
- 75% of addicts are in the workforce
- Only 9% of Americans who need treatment receive it
- New medications can help control craving
- Relapse is a normal part of the disease
- Treatment can work

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### SUBSTANCE RELATED PROBLEMS

- 3rd leading cause of death in U.S.
- Alcoholism causes 80% of cases of hepatic cirrhosis
- Increased incidence of HIV/STD
- Patients injured while under the influence fill 50% of U.S. trauma beds

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### 7 of the 10 Leading Causes of Disability in the World

- Major Depressive Disorder
- Traffic accidents (often substance-related)
- Alcohol Use
- Self-inflicted injuries
- Bipolar disorders
- Violence
- Schizophrenia

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### Alcohol Intoxication

BAL	Consequences
0.02-0.05	Mildly impaired coordination Potential changes in behavior
0.08-0.1	Impaired driving, slurred speech, ataxia, decreased sensory function
0.1-0.15	Impaired balance, gross judgment and cognition impairment
0.2-0.3	All sensory motor function impaired
0.3 & up	Potential cardiovascular and respiratory collapse, <b>coma, death</b>

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### The Neurobiology of Addiction

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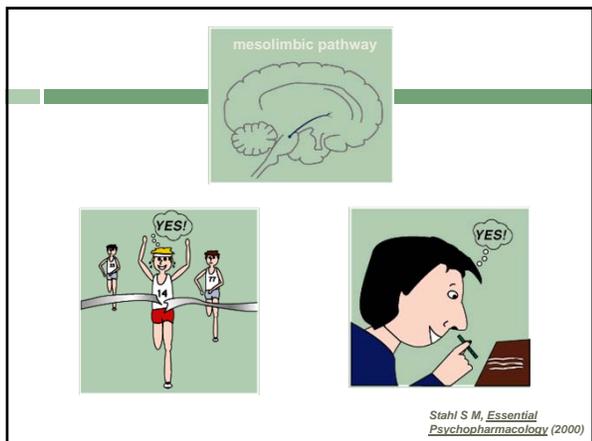
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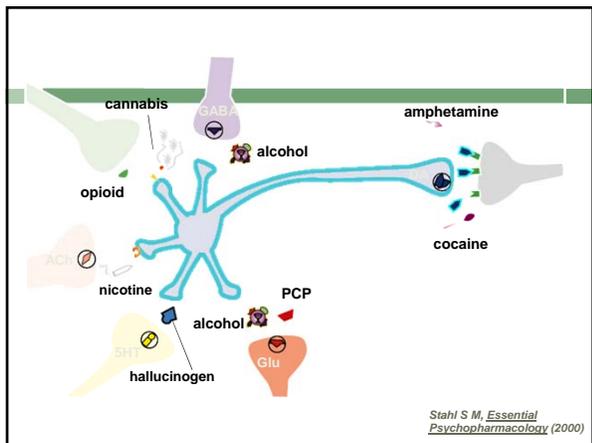
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- ### Drug Categories
- Alcohol
  - Cannabis
  - Cocaine
  - CNS depressants
  - CNS stimulants
  - Opioids
  - Hallucinogens
  - Inhalants
  - Anabolic-androgenic steroids
  - Synthetic
  - OTC
  - Club drugs

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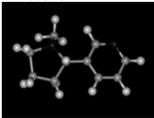
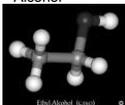
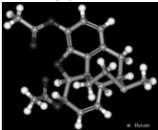
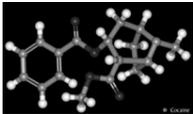
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### Addicting Molecules

<p>Nicotine</p> 	<p>Alcohol</p> 
<p>Heroin</p> 	<p>Cocaine</p> 

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### Is there a single pathway to addiction?

- Drugs of abuse have very different structures and neurotransmitter targets in the brain, but they all exhibit:
  - acute reward
  - chronic reward
  - sensitization
  - negative withdrawal symptoms
  - associative cue learning
  - incentive motivation (relapse)
- A progression from impulsive to compulsive drug use (which defines the progression from abuse into addiction).

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### The Body's Own Psychotropics

- The brain makes its own morphine (beta endorphin) and its own marijuana (anandamide)
- The brain may even make its own antidepressants, anxiolytics, and hallucinogens
- Drugs often mimic the brain's natural neurotransmitters
- Often, drugs are discovered prior to the natural neurotransmitter

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### Exogenous vs. Endogenous Drugs

**We knew about:**

- Morphine before the discovery of  $\beta$ -endorphin
- Marijuana before the discovery of cannabinoid receptors and anandamide
- Valium and Xanax before the discovery of benzodiazepine receptors
- Elavil & Prozac before the discovery of the serotonin transporter site

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## TRANSITION TO ADDICTION

Taking drugs may begin as a voluntary choice to seek a pleasant stimulus, but for addicts, that choice is no longer volitional, even in the face of terrible personal consequences.

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## TOLERANCE, WITHDRAWAL AND DEPENDENCE

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## TOLERANCE

- Dopamine release → Stimulation of receptor
- Stimulation of receptor → Activation of cAMP
- cAMP enters nucleus → Activation of CREB
  - cAMP Response Element Binding protein
- CREB activates Dynorphin
- Dynorphin desensitizes Dopamine Receptor
- Resensitization (Reverse Tolerance)
  - Activation of  $\Delta$  fos B

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## WITHDRAWAL STATES

- Withdrawal syndrome is the predictable constellation of signs and symptoms following abrupt discontinuation of, or rapid decrease in, intake of a substance that has been used consistently for a period of time.
  - Usually the opposite of a substance's direct pharmacologic effects.
- Substances in a given pharmacologic class produce similar withdrawal syndromes
  - The onset, duration, and intensity are variable, depending on the particular agent used, the duration of use, and the degree of neuroadaptation

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## Narcotics

- |                    |               |
|--------------------|---------------|
| □ Rhinorrhea       | • Cramps      |
| □ Yawning          | • Nausea      |
| □ Loss of appetite | • Chills      |
| □ Irritability     | • Diaphoresis |
| □ Tremors          | • Body aches  |
| □ Lacrimation      | • Panic       |

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## Depressants

- Anxiety
- Insomnia
- Tremors
- Delirium
- Seizures
- Possible death

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## Stimulants

- Apathy
- Hypersomnia
- Irritability
- Depression
- Disorientation

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## Cannabis

- Occasional reports of insomnia
- Hyperactivity
- Decreased appetite

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## Hallucinogens

- Unknown

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## Club Drug Facts

Name	Class	Street Name	Desired Effect	Risks
MDMA	Stimulant	Ecstasy Adam Rollies	Euphoria Energy	Tachycardia ↓ serotonin
GHB	Sedative	Georgia-Home Boy Liquid XTC EZ Lay	Relaxation and well-being	Post-use anxiety
Cannibicyclohexinol	Synthetic Cannabinoid	K2 Spice Kronic	Relaxation and well-being	akathisia, tremor, palpitations, headache, nausea, vomiting, depression
Ketamine	NMDA Antagonist	Special K "K" Cat Vallum	Vivid dreams & hallucinations	Dissociation
Mephadrone	Synthetic Stimulant	Plant Food Bath Salts	Euphoria Hyperactivity	Post-use depression and violence Teeth grinding
LSD	Hallucinogen	Acid	Hallucinations	Post-use flashbacks

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## Post-Acute Withdrawal Syndrome

- PAWS
- Anxiety
- Depression
- Autonomic Instability
- Insomnia/hypersomnia
- Drug cravings
- Poor concentration/attention deficits

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## DEPENDENCE

“A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by 3 (or more) of 7 criteria, occurring in the same 12-month period.”

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## Dependence (con't)

### Physiological Dependence

Evidence of tolerance  
or withdrawal (1 & 2)

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## Dependence (con't)

### Psychological Dependence

#### The “3 C’s”

- Loss of Control
- Compulsive Use
- Consequences of Use

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### Dependence (con't)

#### LOSS OF CONTROL

- (3) "Substance taken in larger amounts or over a longer period than intended."
- (4) "Unsuccessful efforts to cut down or control substance use."

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### Dependence (con't)

#### COMPULSIVE USE

- (5) "Great deal of time spent obtaining the substance, using the substance, or recovering from its effects."
- (6) "Important social, occupational, or recreational activities given up or reduced because of substance use."

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### Dependence (con't)

#### CONSEQUENCES OF USE

- (7) "Continued substance use despite knowledge of a persistent or recurrent physical or psychological problem caused or exacerbated by substance use."

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## The Progression of Addiction

- During the initial stages of addiction
  - The pleasure derived from various drugs' activation of the brain's natural reward system promotes continued drug use
- Repeated exposure to drugs induces the brain mechanism of **dependence**
- Dependence leads to daily drug use to avert the unpleasant symptoms of drug withdrawal
- Further prolonged use of drugs lead to more long-lasting changes in the brain that may underlie the compulsive drug-seeking behavior and related adverse consequences that are the hallmarks of addiction.

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## The Important Role of Stress

- Stressors can trigger drug craving in addicts.
  - Sinha R, Catapano D & O'Malley S. (1999). Stress-induced craving and stress response in cocaine dependent individuals. *Psychopharmacology*, 142, 343-351.
- One explanation is that abused drugs raise levels of cortisol which plays a primary role in stress responses.
- Cortisol raises the level of activity in the mesolimbic reward system.
  - Kreek MJ & Koob GF. (1998). Drug dependence: Stress and dysregulation of brain reward pathways. *Drug & Alcohol Dependence*, 51(1-2), 23-47.
- By these mechanisms, stress may contribute to the abuser's desire to take drugs in the first place, as well as the subsequent compulsion to keep taking them.

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## Chemical Dependence: A Complex Genetic Disease

- 40% - 60% of all the possible causes of chemical dependence relate to genetic vulnerability.
  - Having the genes for chemical dependency does not mean that the person will develop the disease
    - There are unknown non-genetic contributing factors that account for the remaining 40-plus percent causes of chemical dependence.
    - Genetic and environmental factors probably interact to result in disease development.
- Chemical dependence is genetically heterogeneous.
  - Multiple genes and alleles are involved

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# BIOLOGIC MODELS OF ADDICTION

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## The 'Changed Set Point' Model

- There are several variants of this model based on the altered neurobiology of:
  - Dopamine neurons in the VTA
  - Norepinephrine neurons in the LC
- These alterations occur during the early phases of withdrawal and abstinence.
- The basic tenet is that drug abuse alters a biological or physiological setting or baseline.

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## The 'Changed Set Point' Model

- Variant #1
  - Neurons of the mesolimbic reward pathways are naturally "set" to release enough DA in the N-Ac to produce a normal level of pleasure.
  - Abused drugs cause addiction by initiating a vicious cycle of changing this set point
    - The release of DA is reduced when normally pleasurable activities occur and the abused drugs are not present
    - A change in the set point occurs in the LC, but in the opposite direction, so NE release is increased during withdrawal accounting for the drug withdrawal aspects of addiction

■ Koob GF & LeMoal M. (2001). Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharmacology*, 24, 97-129.

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### The 'Changed Set Point' Model

- Variant #2
  - DA neurons can become dysfunctional through an alteration of their baseline ("resting") levels of electrical activity and DA release.
    - The resting level is the result of two factors that influence the amount of resting DA release in the N-Ac
      - Cortical excitatory (glutamate) neurons that drive the VTA DA neurons to release DA
      - Autoreceptors ("brakes") that shut down further release when DA concentrations become excessive
  - With continued drug use, there is an increase in number and strength of autoreceptors.
  - When drug use stops, DA deprivation results, manifesting in dysphoria (pain, agitation, malaise) & other w/d symptoms
    - Grace AA. (2000). The tonic/phasic model of dopamine system regulation and its implications for understanding alcohol and stimulant craving. *Addiction*, 95(Suppl 2), S119-S128.

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### The 'Changed Set Point' Model

- Variant #3
  - Emphasizes the sensitivity to environmental cues that leads to drug wanting or craving.
    - During periods when the drug is not available to addicts, their brains can remember the drug, and desire or craving for the drug can be a major factor leading to relapse.
      - This craving may represent increased activity of glutamate and NE
        - This leads to drug craving and increased withdrawal symptoms.
          - Robinson TE & Berridge KC. (2000). The psychology and neurobiology of addiction: An incentive-sensitization view. *Addiction*, 95(Suppl 2), S91-S117.

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### Types of Craving

- Cue-based craving
  - Response to environmental cue
  - Cue creates internal state which is recognized as craving
  - Most notable in cocaine & nicotine
- State or stress-based craving
  - Emotional tone, level of perceived stress, state of self care set the state
  - Craving appears to emerge out of difficult emotional states
  - Most notable in alcohol & sedatives

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### The Cognitive Deficits Model

- Proposes that individuals who develop addictive disorders have abnormalities in the prefrontal cortex.
  - The PFC is important for regulation of judgment, planning, and other executive functions.
    - Normally , the PFC sends inhibitory signals to the VTA DA neurons of the mesolimbic reward system to help overcome some of our impulses for immediate gratification.
  - Stimulant drugs appear to damage the specific brain circuit (frontostriatal loop) that carries inhibitory signals from the PFC to the mesolimbic reward system
  - Chronic alcohol abusers have abnormally low levels of GABA, the neurochemical that the PFC uses to signal the reward system to release DA.
  - Opiates apparently damage the PFC itself.

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### Thank You For Participating

COMMENTS  
AND  
QUESTIONS

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