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

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
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

Alcohol Intoxication

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

The Neurobiology of Addiction
Drug Categories
- Alcohol
- Cannabis
- Cocaine
- CNS depressants
- CNS stimulants
- Opioids
- Hallucinogens
- Inhalants
- Anabolic-androgenic steroids
- Synthetic
- OTC
- Club drugs
Addicting Molecules

Nicotine  Alcohol  Heroin  Cocaine

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).

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
**Exogenous vs. Endogenous Drugs**

**We knew about:**

- Morphine before the discovery of β-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

**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.

**TOLERANCE, WITHDRAWAL AND DEPENDENCE**
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 Δ fos B

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

Narcotics

- Rhinorrhea
- Yawning
- Loss of appetite
- Irritability
- Tremors
- Lacrimation
- Cramps
- Nausea
- Chills
- Diaphoresis
- Body aches
- Panic
Depressants
- Anxiety
- Insomnia
- Tremors
- Delirium
- Seizures
- Possible death

Stimulants
- Apathy
- Hypersomnia
- Irritability
- Depression
- Disorientation

Cannabis
- Occasional reports of insomnia
- Hyperactivity
- Decreased appetite
Hallucinogens

- Unknown

Club Drug Facts

<table>
<thead>
<tr>
<th>Name</th>
<th>Class</th>
<th>Street Name</th>
<th>Desired Effect</th>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDMA</td>
<td>Stimulant</td>
<td>Adam Rolls</td>
<td>Euphoria</td>
<td>Tachycardia, serotonin</td>
</tr>
<tr>
<td>GHB</td>
<td>Sedative</td>
<td>Georgia-Home Boy, Liquid XTC, EZ Lay</td>
<td>Relaxation and well-being</td>
<td>Post-use anxiety</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>Synthetic Cannabinoid</td>
<td>K2, Space Inc., Space Venice</td>
<td>Relaxation and well-being</td>
<td>Hallucinations, dissociation</td>
</tr>
<tr>
<td>Ketamine</td>
<td>NMDA Antagonist</td>
<td>Special K, &quot;K&quot;</td>
<td>Void dreams &amp; hallucinations</td>
<td>Dissociation</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>Synthetic Stimulant</td>
<td>Party Patch, Bath Salts</td>
<td>Euphoria, hyperactivity</td>
<td>Post-use depression and violence, teeth grinding</td>
</tr>
<tr>
<td>LSD</td>
<td>Hallucinogen</td>
<td>Acid</td>
<td>Hallucinations</td>
<td>Post-use flashbacks</td>
</tr>
</tbody>
</table>

Post-Acute Withdrawal Syndrome

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

Dependence (con’t)

Physiological Dependence

Evidence of tolerance or withdrawal (1 & 2)

Dependence (con’t)

Psychological Dependence

The “3 C’s”

• Loss of Control
• Compulsive Use
• Consequences of Use
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.”

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.”

CONSEQUENCES OF USE
- (7) “Continued substance use despite knowledge of a persistent or recurrent physical or psychological problem caused or exacerbated by substance use.”
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.

The Important Role of Stress

- Stressors can trigger drug craving in addicts.
- 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.
- 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.

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
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.

- 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

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


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.


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
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.

Thank You For Participating

COMMENTS AND QUESTIONS

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