The Science of Drug Addiction: Implications for Clinical Practice

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Chief Resident Immersion Training Program
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The Many Faces of Addiction
Today’s Topics

• Trends in Substance Use
• Understanding Addiction
• NIDA Priority Areas
  – Prevention
  – Treatment
  – Health Consequences
• Resources
Trends in Substance Use
“Addiction” Diagnosis ~ 23,000,000
In Specialty Treatment ~ 2,300,000
“Harmful Use” ~ 60,000,000
Rare Use
Little or No Use

Source: A. T. McLellan, 2011

Scope of Substance Use in the U.S.
Question:

What is the most widely used drug by teens?
### Drugs Frequently Abused by U.S. Teens

<table>
<thead>
<tr>
<th>Drug</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>63.5%</td>
</tr>
<tr>
<td>Marijuana/Hashish</td>
<td>36.4%</td>
</tr>
<tr>
<td>Small Cigars</td>
<td>19.9%</td>
</tr>
<tr>
<td>Hookah</td>
<td>18.3%</td>
</tr>
<tr>
<td>Synthetic Marijuana</td>
<td>11.3%</td>
</tr>
<tr>
<td>Snus (tobacco)</td>
<td>7.9%</td>
</tr>
<tr>
<td>Prescription Opioids</td>
<td>7.9%</td>
</tr>
<tr>
<td>Amphetamines*</td>
<td>7.9%</td>
</tr>
<tr>
<td>Tranquilizers</td>
<td>5.3%</td>
</tr>
<tr>
<td>Cough Medicine</td>
<td>5.6%</td>
</tr>
<tr>
<td>Hallucinogens</td>
<td>4.8%</td>
</tr>
<tr>
<td>Sedatives*</td>
<td>4.5%</td>
</tr>
<tr>
<td>Salvia</td>
<td>4.4%</td>
</tr>
<tr>
<td>MDMA (Ecstasy)</td>
<td>3.8%</td>
</tr>
<tr>
<td>Inhalants</td>
<td>2.9%</td>
</tr>
<tr>
<td>Cocaine (any form)</td>
<td>2.7%</td>
</tr>
</tbody>
</table>

Monitoring the Future study, 2011
Question:

What’s Molly?
Shifting Landscape of Drug Abuse Over Time

% Students Reporting Any Illicit Drug Use in Past Year, by Grade

SOURCE: University of Michigan, 2011 Monitoring the Future Study
Relative Shifts in Prevalence

% Students Reporting Past Month Marijuana and Cigarettes (by Grade)

SOURCE: University of Michigan, 2011 Monitoring the Future Study
Percentage of U.S. 12th Grade Students Reporting Past Month Use of Cigarettes and Marijuana

SOURCE: 2013 Monitoring the Future Study
Changes in Attitude Lead to Changes in Use: Marijuana Use and Perceived Risk in 12th Graders

Source: Monitoring the Future, 2011
Synthetic Drugs

% of Students Reporting Synthetic Marijuana Use Annually (by Gender)

SOURCE: University of Michigan, 2011 Monitoring the Future Study
Drug Overdose Death Rates in USA More Than Tripled Since 1990 (Nearly 17,000 in 2010).

More OD Deaths than MVA Deaths Since 2009

Motor vehicle traffic, poisoning, and drug poisoning (overdose) death rates: United States, 1980-2010
Increases in Opioid Deaths Parallel Opioid Sales and Treatment Admissions

- Opioid Sales KG/10,000
- Opioid Deaths/100,000
- Opioid Treatment Admissions/10,000

National Vital Statistics System, DEA’s Automation of Reports and Consolidated Orders System, SAMHSA’s TEDS
Question:

What medical specialties prescribe the most opioid medications to youth?
Opioid Medication Prescribers by Specialty

Source: IMS Vector ©One National, TPT 06-30-10 Opioids Rate 2009
## Estimated Economic Cost to Society Due to Substance Use Disorders

<table>
<thead>
<tr>
<th>Substance</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco</td>
<td>$193 billion/year</td>
</tr>
<tr>
<td>Alcohol</td>
<td>$235 billion/year</td>
</tr>
<tr>
<td>Illegal drugs</td>
<td>$181 billion/year</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>$609 billion/year</strong></td>
</tr>
</tbody>
</table>

Source: CDC, 2007; Rehm et al., 2009 Lancet 373:2223-33
Understanding Addiction
Advances in neuroscience have revolutionized our fundamental understanding of drug abuse and addiction.
this is your brain on drugs.
The Brain on Drugs

YELLOW shows places in brain where cocaine binds (Striatum)

Front of brain

1-2 Min
3-4
5-6

Back of brain

6-7
7-8
8-9

9-10
10-20
20-30
Addiction is a Disease of the Brain

Decreased Brain Metabolism in **SUD Patient**

Decreased Heart Metabolism in **Heart Disease Patient**

Sources: From the laboratories of Drs. N. Volkow and H. Schelbert
Addiction is Like Many Other Diseases

• Addiction is preventable
• Addiction is treatable
• Recovery is possible
NIDA Priority Areas

**Prevention**
- Genetics
- Environment
- Development

**Treatment**
- Neural mechanisms
- Brain circuitry

**Consequences**
- HIV/AIDS
- Fetal Exposure
Why do some people become addicted to drugs while others do not?
Addiction Prevalence Varies by Drug

Estimated Prevalence of Dependence Among Users

Source: Anthony JC et al., 1994
Development of Addiction Involve Multiple Factors

- Biology (Genes/Development)
- Environment

DRUG/ALCOHOL USE

Brain Mechanisms

Addiction
Susceptibility to Addiction Results from Interaction of Many Genes

- **FAAH** - associated with drug dependence
- **OPRM1** - associated with opiates and alcoholism
- **CYP2A6, CYP2B6** - associated with smoking and smoking cessation
- **ALDH2** - associated with protection against alcoholism
- **DBH** (Dopamine beta-hydroxylase) – cocaine-induced paranoia
- **DRD2, DRD4** (Dopamine receptors) - reward, craving
- **NrCAM, neurexins** (Cell adhesions genes) - assoc with drug abuse and addiction
- **Prodynorphin gene** - associated with protection against cocaine dependence
- **Nicotinic alpha 7 promoter** – assoc. with decreased expression of its message in different brains regions and with sensory gating defects in schizophrenics
- **Alpha 5 and beta 3** (nicotinic receptors) – assoc. with nicotine dependence
- **5HT1B** (serotonin receptor) - associated with conduct disorder and alcoholism
Genetic Variability and Effects of Drugs

Genetic variation in COMT influences the harmful effects of abused drugs.

% with schizophreniform disorder at age 26

- No adolescent cannabis use
- Adolescent cannabis use

What Environmental Factors Contribute to Addiction?

- Drug availability
- Peers who use drugs
- Family Problems
- Early physical or sexual abuse
- Stress in general
Effects of a Social Stressor on Brain Dopamine D2 Receptors and Propensity to Administer Drugs

Individually Housed

Group Housed

Becomes Dominant
No longer stressed

Becomes Subordinate
Stress remains

Social Setting Can Change Neurobiology

Reinforcers (per session)

Cocaine (mg/kg/injection)

ACE is associated with $\frac{1}{2}$ to $\frac{2}{3}$ of serious problems with drug use.

Addiction Is Developmental

Age of Onset of Drug Abuse and Dependence

The brain continues to develop until what age?
The Adolescent Brain

- Brain develops till mid/late 20s!
- Pre-frontal cortex last to develop
- Age of drug use onset is predictor of later life drug problems
- 15% of those who start drinking by age 14 develop problems as adults (vs 2% who wait till age 21)
What Does Science Tell Us About Effective Prevention Programs?

National Institute on Drug Abuse

Preventing Drug Use among Children and Adolescents

A Research-Based Guide for Parents, Educators, and Community Leaders

Second Edition
# Examples of Risk and Protective Factors

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Domain</th>
<th>Protective Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Aggressive Behavior</td>
<td>Individual</td>
<td>Self-Control</td>
</tr>
<tr>
<td>Poor Social Skills</td>
<td>Individual</td>
<td>Positive Relationships</td>
</tr>
<tr>
<td>Lack of Parental Supervision</td>
<td>Family</td>
<td>Parental Monitoring and Support</td>
</tr>
<tr>
<td>Substance Abuse</td>
<td>Peer</td>
<td>Academic Competence</td>
</tr>
<tr>
<td>Drug Availability</td>
<td>School</td>
<td>Anti-Drug Use Policies</td>
</tr>
<tr>
<td>Poverty</td>
<td>Community</td>
<td>Strong Neighborhood Attachment</td>
</tr>
</tbody>
</table>

**Effective Prevention Programs**

- Reduce these
- Elevate these
Nurse Home Visiting Program (prenatal-age 2)

Percent of Children Who Used Tobacco, Alcohol, or Marijuana (Last 30 Days)  
Child Age 12

Percent of Children with Internalizing Problems (Borderline or Clinical)  
Child Age 12

PIAT Scores - Reading & Math – Age 12  
(Born to Low-Resource Mothers)

Percent of Mothers with Role Impairment due to Alcohol or Drug Use – Child Age 12

Arch Pediatr Adolesc Med, 164(5) 412-418, 2010
NIDA Priority Areas

**Prevention**
- Genetics
- Environment
- Development

**Treatment**
- Neural mechanisms
- Brain circuitry

**Consequences**
- HIV/AIDS
- Fetal Exposure
Neuronal Circuits Involved In Drug Abuse and Addiction

EXECUTIVE FUNCTION/INHIBITORY CONTROL

MOTIVATION/DRIVE

REWARD

MEMORY/LEARNING

- OFC
- SCC
- PFC
- ACG
- OFC
- Hipp
- NAcc
- VP
- Amy g
1. **Reward Circuit**

Drugs of Abuse Engage Systems in the Motivation Pathways of the Brain
Natural Rewards Elevate Dopamine Levels

Drugs Elevate Dopamine Levels More/Longer

- **AMPHETAMINE**: Hrs. after amphetamine
- **COCAINE**: Hrs. after cocaine
- **NICOTINE**: Hrs. after nicotine
- **MORPHINE**: Hrs. after morphine

Source: Di Chiara and Imperato
The Neuron: How the Brain’s Messaging System Works
dopamine transporters
Dopamine Receptors Lower in Addiction

- Cocaine
- Alcohol
- Heroin

control | addicted

DA D2 Receptor Availability
Increased interaction between proteins in the nucleus accumbens may result in enhanced responsiveness (reward) to cocaine.

Bonci, et al (2013), *Cell*
2. Memory circuit

“People, places and things…”
Cocaine Craving:
Population (Cocaine Users, Controls) x Film (cocaine)

Garavan et al A. J. Psych 2000
Cocaine Craving:
Population (Cocaine Users, Controls) x Film (cocaine, erotic)

Garavan et al A.J. Psych 2000

Controls  Cocaine Users

Signal Intensity (AU)

Cingulate

Ant Cing

IFG
Even Unconscious Cues Can Elicit Brain Responses

Brain Regions Activated by 33 millisecond cocaine cues (too fast for conscious recognition)

Childress, et al., PLoS ONE 2008
Dopamine is also associated with motivation and executive function via regulation of frontal activity.
The fine balance in connections that normally exists between brain areas active in reward, motivation, learning and memory, and inhibitory control becomes severely disrupted in addiction.
Non-Addicted Brain

- Control
- CG
- Drive
- OFC

Addicted Brain

- Control
- Drive
- Memory

Saliency
- NAc
- Amygdala

STOP

GO
Partial Recovery of Brain Dopamine Transporters in Abuser After Protracted Abstinence

### Behavioral Treatments

#### Non-Addicted Brain

- **Saliency**
- **Drive**
- **Memory**

#### Behavioral Therapies

- **Interfere with drug’s reinforcing effects**
- **Strengthen prefrontal-striatal communication**
- **Interfere with conditioned memories**
- **Teach new memories**
- **Counteract stress responses that lead to relapse**

#### Cognitive Therapy

- **Executive function/Inhibitory control**

#### Motivation Therapies

- **Contingency Management**
- **Biofeedback Desensitization**
- **Behavioral Therapies**
- **Relaxation Behavioral therapies**
Medication Assisted Treatments

Non-Addicted Brain

- Control
- Drive
- Memory

STOP

Interfere with drug’s reinforcing effects
- Vaccines
  - Enzymatic degradation
  - Naltrexone
  - DA D3 antagonists
  - CB1 antagonists

Executive function/
Inhibitory control
- Biofeedback
  - Modafinil
  - Bupropion
  - Stimulants

Strengthen prefrontal-
striatal communication
- Adenosine
  - A2 antagonists
  - DA D3 antagonists

Interfere with conditioned memories
- Antiepileptic GVG
  - N-acetylcysteine

Teach new memories
- Cycloserine

Counteract stress responses that lead to relapse
- CRF antagonists
  - Orexin antagonists
Vivitrol Significantly Increases % of Patients with Opioid-free Weeks
A Double-Blind RCT of N-Acetylcysteine in Cannabis-Dependent Adolescents

Proportion of Negative Urine Cannabinoid Tests Over Time Among Cannabis-Dependent Adolescents

Extended-Release Mixed Amphetamine Salts and Topiramate for Cocaine Dependence

Combination of MAS-ER and topiramate was superior to placebo in achieving 3 week abstinence in cocaine-dependent individuals

Mariani et al., Biol Psychiatry 2012
Genetic Variability and Personalized Treatment

Genetics can help predict the outcome of treatment for alcohol dependence.

adapted from Oslin et al. *Neuropsychopharmacology*, 2003
Anti-Drug Vaccine Development

Capillary Blood Flow

Antibody holds drug in bloodstream
Cutting Edge Research:
Targeted Stimulation of the Pre-frontal Cortex as a Promising Treatment for Cocaine Addiction

Optogenetic stimulation results in:
- reduced cocaine-seeking in addicted rats
- increased cocaine seeking in non-addicted rats

-Evidence for a cocaine-induced deficit within a brain region involved in addictive disorders

-Rapid translation to clinical human trials via non-invasive brain stimulation

Translating Research into Practice

Access and Engagement

Provider knowledge and behavior

Organization Structure and Climate

External Environment (stigma, financing)
Receipt of SUD Services Lags Behind other Chronic Disorders

- Any Mental Illness: 45.9 million, 39.2% receiving treatment
- Substance Use Disorder: 23.1 million, 11.2% receiving treatment
- Diabetes: 25.8 million, 84% receiving treatment
- Heart Disease: 81.1 million, 74.6% receiving screenings
- Hypertension: 74.5 million, 70.4% receiving treatment
Low Uptake of Pharmacotherapy in Specialty Programs in 2007

<table>
<thead>
<tr>
<th></th>
<th>As % of all programs surveyed (N=345)</th>
<th>Within adopting programs, % of eligible patients receiving Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric meds</td>
<td>54.5</td>
<td>70.1</td>
</tr>
<tr>
<td>Opioid tx meds:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>7.8</td>
<td>41.3</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>20.9</td>
<td>37.3</td>
</tr>
<tr>
<td>Tablet naltrexone</td>
<td>22.0</td>
<td>10.9</td>
</tr>
<tr>
<td>Alcohol meds:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disulfiram</td>
<td>23.8</td>
<td>8.1</td>
</tr>
<tr>
<td>Tablet naltrexone</td>
<td>32.2</td>
<td>12.4</td>
</tr>
<tr>
<td>Acamprosate</td>
<td>32.5</td>
<td>17.5</td>
</tr>
<tr>
<td>Injectable naltrexone</td>
<td>15.9</td>
<td>(too new to report)</td>
</tr>
</tbody>
</table>

Medications and Criminal Justice Populations

Methadone Experiment: 6 Mo Post Release (N=201)

Affordable Care Act (ACA)

- Extends coverage to more than 30 million persons, many at high risk for drug abuse
- Promotes use of electronic health records
- Fundamentally changes the ways drug abuse prevention and treatment services are financed
- Focuses on screening and prevention
- Emphasizes central role of primary care settings
NIDA Priority Areas

Prevention
- Genetics
- Environment
- Development

Treatment
- Neural mechanisms
- Brain circuitry

Consequences
- HIV/AIDS
- Fetal Exposure
HAART as HIV Prevention

Montaner et al., Lancet 2008

NIDA Avant Garde 2008: Dr. Julio Montaner, Univ. of British Columbia
Resources
• Centers of Excellence
  – Boston University
  – Drexel/University of Pennsylvania
  – University of Massachusetts
  – Tufts University
  – University of North Dakota
  – Creigton University

• Screening tools

• CMEs on prescription drug abuse
The Clinical Assessment of Substance Use Disorders
Innovative E-Learning Rx Drug Abuse CME:
NIDA and Medscape, Funded by ONDCP, October 2012

Safe Prescribing for Pain

Managing Pain Patients Who Abuse Rx Drugs
Any Questions?

• Jack.stein@nih.gov
So, what’s going on with Marijuana??
Shifting policy landscape
Marijuana is the Most Commonly Used Illicit Drug in the U.S.

- Over 111 million Americans have tried it at least
- An estimated 2.4 million Americans used it for the first time in 2012

Tetrahydrocannabinol (THC) = Active Ingredient in Marijuana

Source: 2012 National Survey on Drug Use and Health, SAMHSA
Average Delta-9 THC Concentration Per Year

Source: University of Mississippi
The Marijuana Farm: University of Mississippi
12th Graders’ Past Year Marijuana Use vs. Perceived Risk of Occasional Marijuana Use

SOURCE: University of Michigan, 2013 Monitoring the Future Study
Source of Marijuana* among 12th Graders in 2012 and 2013, by State Policy

**Categories not mutually exclusive**

**Statistically significant difference**

*Medical Marijuana States* | *Non-Medical Marijuana States*

SOURCE: University of Michigan, 2013 Monitoring the Future Study
Cannabinoid Receptors Are Located Throughout the Brain and Regulate:

- Brain Development
- Memory and Cognition
- Motivational Systems & Reward
- Appetite
- Immunological Function
- Reproduction
- Movement Coordination
- Pain Regulation & Analgesia
Marijuana: What’s the harm?

- Addiction
- Motor Vehicle Accidents
- Motivation, Mood, Paranoia, Psychosis
Marijuana addiction is also linked to a withdrawal syndrome that can make it hard to quit. Symptoms include:

- irritability,
- sleeping difficulties,
- craving,
- anxiety, and
- increased aggression.

Marijuana withdrawal is now recognized in DSM-5.