Advances in Drug Abuse and Addiction from NIDA: Implications for Treatment

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NIDA Research
From Molecules...
...To Managed Care
...Drug Courts
...Community Coalitions

Advances in Science Are Bringing Us New Understanding of Drug Abuse & Addiction
AND...
This Knowledge Is Allowing Us To Develop More Targeted Strategies for Its Prevention and Treatment
Priority Areas for NIDA

- Prevention Research (Children and Adolescents)
  - genetics
  - development
  - environment
  - co-morbidity
- Treatment Interventions (New Targets)
- HIV/AIDS Research
- Training Researchers

What have we learned?
What have we learned about Vulnerability?

Why do some people become addicted while others do not?

Drug Abuse Risk Factors

Community
Peer Cluster
Family
Individual
We Know There’s A Big Genetic Contribution To Drug Abuse and Addiction…
And the Nature of this Contribution Is Extremely Complex

### Genetic component of common traits

<table>
<thead>
<tr>
<th>Trait</th>
<th>Heritability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 (adult-onset) diabetes</td>
<td>0.3</td>
</tr>
<tr>
<td>Type 1 (insulin-dependent) diabetes</td>
<td>0.7</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.3 – 0.5</td>
</tr>
<tr>
<td>Peanut allergy</td>
<td>0.8</td>
</tr>
<tr>
<td>Cataract (age-related)</td>
<td>0.5</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>0.6</td>
</tr>
<tr>
<td>Nicotine</td>
<td>0.5 – 0.6</td>
</tr>
<tr>
<td>Cocaine and stimulants</td>
<td>0.4 – 0.5</td>
</tr>
<tr>
<td>Heroin and opiates</td>
<td>0.5</td>
</tr>
<tr>
<td>Marijuana</td>
<td>0.3 – 0.8</td>
</tr>
</tbody>
</table>
Some Genes associated with Drug Abuse:

- CYP2A6: tobacco dependence
- FAAH (endogenous cannabinoid regulator): problem drug use
- Mu-opioid receptor: in heroin addiction

DA Receptor Levels and Response to MP

Subjects with low receptor levels found MP pleasant while those with high levels found MP unpleasant.

High Levels of Dopamine D2 Receptors May Provide Protection Against Alcoholism in Unaffected Members of Alcoholic Families

Researchers also found that increased D2 receptors in the family positive subjects correlated with metabolism in the frontal regions and with positive emotionality.
Genetic Variation Predicts Naltrexone Treatment Response for Alcohol Dependence

Cumulative Survival (Time to Relapse)

Days

Naltrexone/Asp40 Allele (A/G, G/G) (n=23)
Naltrexone/Asn40 Allele (A/A) (n=48)
Placebo/Asn40 Allele (A/A) (n=41)
Placebo/Asp40 Allele (A/G, G/G) (n=18)


Genetics

Gene/Environment Interaction

What have we learned about other aspects of vulnerability?
Drug Addiction is a Developmental Disease that Starts in Adolescence and Childhood

Addiction Is a Developmental Disease starts in childhood and adolescence

The Adolescent Brain Is Still Undergoing Development

Brain areas where volumes are smaller in adolescents than young adults

During Adolescence the COGNITION-EMOTION Connection is Still Forming
When Reading Emotion,…
Adults Rely More on Frontal Cortex
Teens Rely More on the Amygdala

Killgore et al., NeuroReport, v12(2), 2001

Frontal and Amygdalar Activity Differ in Adults and Adolescents

Yurgelun-Todd et al., Percept Mot Skills, 99:2, 2004

Correlation Between Age and PFC Activity During Fear Face Processing

Frontal Activation Increases with Age

When Reading Emotion,…
Frontal Activation decreases with Age

When Reading Emotion,…
Adults exhibit More PFC Activity
Teens exhibit More Amygdalar Activation


Right Lateral and Top Views of the Dynamic Sequence of GM Maturation Over the Cortical Surface

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• Exposure to drugs of abuse during adolescence could have profound effects on Brain Development & Brain Plasticity.

• Understanding drug abuse and addiction from a Development Perspective has important implications for their Prevention & Treatment.

The Adolescent Brain Responds to Drugs Differently than the Adult Brain

Treatment of adolescent rats (but not young adults) with Nicotine leads to

Increases in Nicotine Self Administration

Increases in Nicotine Receptors

Adolescent Exposure to Cannabinoids Alters the Response of VTA Dopamine Neurons to Drugs of Abuse


Source: Abdania, W. et al., J of Neurosci, 23(11), pp. 4712-4716, June 1, 2003.

Increases in Nicotine Receptors

Percent baseline firing rate

Vehicle pretreated
CB adolescent
CB adult

Morphine (mg/kg)

Cocaine (mg/kg)

Morphine (mg/kg)

Amphetamine (mg/kg)
ADDICTIVE DISORDERS OFTEN CO-EXIST WITH MENTAL DISORDERS

Results: Lifetime Disorders

<table>
<thead>
<tr>
<th></th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>Any Alcohol</td>
<td>36.3</td>
</tr>
<tr>
<td>Any Drug</td>
<td>10.3</td>
</tr>
<tr>
<td>Any Mood</td>
<td>19.5</td>
</tr>
<tr>
<td>Any Anxiety</td>
<td>16.2</td>
</tr>
<tr>
<td>Antisocial Personality</td>
<td>3.6</td>
</tr>
</tbody>
</table>

Source: Results from the 2001-2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)

Lifetime Mood Disorders Among Those with Drug Disorders

<table>
<thead>
<tr>
<th></th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>Any Mood</td>
<td>46.2</td>
</tr>
<tr>
<td>Major Depression</td>
<td>33.2</td>
</tr>
<tr>
<td>Dysthymia</td>
<td>11.4</td>
</tr>
<tr>
<td>Mania</td>
<td>12.0</td>
</tr>
<tr>
<td>Hypomania</td>
<td>4.7</td>
</tr>
</tbody>
</table>

Source: Results from the 2001-2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)
Lifetime Anxiety Disorders Among Those with Drug Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Anxiety</td>
<td>29.9</td>
</tr>
<tr>
<td>Panic with Agoraphobia</td>
<td>3.6</td>
</tr>
<tr>
<td>Panic without Agoraphobia</td>
<td>9.0</td>
</tr>
<tr>
<td>Social Phobia</td>
<td>10.7</td>
</tr>
<tr>
<td>Specific Phobia</td>
<td>17.1</td>
</tr>
<tr>
<td>Generalized Anxiety</td>
<td>9.2</td>
</tr>
</tbody>
</table>

Source: Results from the 2001-2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)

Smoking and Mental Illness

- 44% of all cigarettes consumed in the US are by individuals with a current psychiatric disorder
- 75% of patients in addiction and mental health treatment programs smoke cigarettes

Source: Lasser, K et al., JAMA 284(20), November 22/29, 2000.

Comorbidity is a Reality
What have learned about how drugs work?

Activation of the reward pathway by addictive drugs

Natural Rewards Elevate Dopamine Levels

Source: Di Chiara et al.

Source: Fiorino and Phillips
Prolonged Drug Use Changes
The Brain In Fundamental and
Long-Lasting Ways

AND...

We Have Evidence That
These Changes Can Be Both
Structural and Functional

Dopamine D2 Receptors are Lower in Addiction
Normal responses to drugs

Use-dependent plasticity leading to sensitized responses to drug and environmental cues

Repeated drug exposure
(e.g., via neurotrophic factors, ΔFosB, CREB?)

Chronic cocaine increases density of dendritic spines and neuronal branching in the nucleus accumbens

Repeated Drug Abuse Increases Genetic Transcription Resulting in Long-term Structural Changes

Adapted from Nestler E.J. Science & Practice Perspectives, 5(1) 2005.
AND...

We Have Evidence That
These Changes Can Be Both
*Structural* and *Functional*

**Dopamine Transporters in Methamphetamine Abusers**

Normal Control

Methamphetamine Abuser

**Motor Task**
Loss of dopamine transporters in the meth abusers may result in slowing of motor reactions.

**Memory Task**
Loss of dopamine transporters in the meth abusers may result in memory impairment.
We Do Know that the Brain Circuitry Involved in Addiction Has Similarities to that of Other Motivational Systems.
Cocaine Craving:
Population (Cocaine Users, Controls) x Film (cocaine, erotic)

This Results in
"Motivational Toxicity" and Compulsive Drug Use (Addiction)

Relapsers and Nonrelapsers Make Decisions Differently
MA abusers who relapse after treatment appear to make decisions using different brain regions than those who remain abstinent (90% accuracy).
Cue-Induced Brain Activity Changes Better Predictor of Relapse in Cocaine-Dependent Patients than Subjective Reports of Craving

Kosten et al., Neuropsychopharmacology (2006) 31, 644-650

Circuits Involved In Drug Abuse and Addiction

Brain Glucose Metabolism in Cocaine Abusers (n = 20) and Controls (n = 23)
Implication:

Brain changes resulting from prolonged use of drugs may be reflected in compromised cognitive functioning

Is there recovery?

ADDICTION CAN BE TREATED

Partial Recovery of Brain Dopamine Transporters in Methamphetamine (METH) Abuser After Protracted Abstinence

We Need to View and Treat Addiction As A Chronic, Relapsing Illness
We Have A Variety Of Effective Treatment Options In The Clinical Toolbox

Some Behavioral Treatments with a Strong Science Base

- Behavioral Treatments for MJ Abuse
- Behavioral Treatments for Smoking Cessation
- Cognitive-Behavioral Treatment
- Combined Pharmacotherapies and Behavioral Therapies
- Multisystemic Therapy
- Contingency Management Treatments*
- Dialectical Behavioral Therapy
- Drug Counseling
- Family Treatments
- Group Behavior Therapy
- HIV Risk Reduction
- Motivational Interviewing/Enhancement*
- Seeking Safety (PTSD)
- Work Therapy

Medications Development

- Methadone
- Naltrexone
- Clonidine
- Buprenorphine
- Bupropion
- NRT
We Have A Variety Of Effective Treatment Options In The Clinical Toolbox

...But We Need To And Can Do Better

Interventions targeting:
  Reward/Saliency
  Motivation
  Relapse (stress, craving, conditioned-cues, other?)
  Inhibitory Control

HIV/AIDS
Drugs of Abuse Have Had A Major Impact on the HIV/AIDS Epidemic

Proportions of AIDS Cases in Adults & Adolescents by Exposure in the USA

Source: Centers for Disease Control and Prevention (CDC)

Men who have sex with men (MSM)
Injection drug use
Heterosexual contact
MSM who inject drugs

Year of Diagnosis

% of Cases

Proportions of AIDS Cases in Adults and Adolescents by Race/Ethnicity in the USA

Source: Centers for Disease Control and Prevention (CDC)

Year of Diagnosis

% of Cases

Drug Addiction Treatment is HIV Prevention

Source: NIDA
So What Will Happen with all this research?

If a Tree Falls in the Forest, and No One Is Around… Does It Really Make a Sound?

If Research is Done and Only Published in Peer Reviewed Journals
that Remain on the Shelves...

Community
↑
Bedside
↑
Bench

TRANSLATIONAL BOTTLENECK

A translational bottleneck. Citations per year based on PUBMED.

Few Treatment Programs Use Treatment Innovations

<table>
<thead>
<tr>
<th>Treatment Innovation</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Buprenorphine</td>
<td>7.3%</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>21.2%</td>
</tr>
<tr>
<td>Nicotine Patch</td>
<td>38.2%</td>
</tr>
<tr>
<td>Acupuncture</td>
<td>9.4%</td>
</tr>
<tr>
<td>Motivational Incentives</td>
<td>15.9%</td>
</tr>
<tr>
<td>Manualized MET</td>
<td>24.7%</td>
</tr>
</tbody>
</table>

N=766 public- and private-sector treatment units, 2004

Source: Roman et al., National Treatment Center Study, 2004

Developing an Evidence-Based-Practice is Only One Piece of the Translation Puzzle

Intervention

Access & Engagement

Organization Structure & Climate

Provider Knowledge & Behavior

External Environment (Stigma, Financing)

What Are We Doing About All of This?

NIDA
Our Strategy Involves BLENDING RESEARCH and PRACTICE

Bringing Science-Based Technologies Into Ongoing Community Practice

Blending Research and Practice

National Drug Abuse Treatment Clinical Trials Network (CTN)

NIDA Criminal Justice Drug Abuse Treatment Studies (CJ-DATS)

A research infrastructure of 37 RRTCs & 240 CTPs across 34 States, and Puerto Rico
CJ-DATS Update
Criminal Justice Drug Abuse Treatment Studies

- 6 studies in the field focused on:
  - Reducing HIV risk behavior
  - Screening for mental illness
  - Transitioning from prison to community
- 2 juvenile justice studies being developed
  - Community re-entry and HIV risk behaviors
- 2 HIV studies being developed:
  - Men
  - Women

www.cjdats.org
NIDA/SAMHSA Blending Initiative

The Blending Initiative encompasses three primary components:

- Blending Conferences
- Blending Teams
- State Agency Partnerships

Research Dissemination & Application: A “Recipe” for Success

- One part CSAT
- One part NIDA
- A pinch of $$$
- Ok... a few more $$$
- Some TLC
- A dash of luck
- Shake vigorously and...
Dissemination Products are Released at the Same Time Research is Published

Create the charge for the Blending Team, based on research results and how it can address critical needs in the treatment field.

Goal is to develop dissemination strategies & products. Each Blending Team is composed of ATTC members & NIDA members.

Dissemination Products are Released at the Same Time Research is Published

Five Blending Teams

1) Buprenorphine Treatment: A Training for Multidisciplinary Addiction Professionals
2) Short-Term Opioid Withdrawal Using Buprenorphine
3) Utilizing the Addiction Severity Index (ASI)
4) Motivational Interviewing Assessment: Supervisory Tools for Enhancing Proficiency (MIA-STEP)
5) Promoting Awareness of Motivational Incentives (PAMI)

Second Component: Blending Teams

Current Status of Product Development

1) Buprenorphine Treatment
2) Buprenorphine Detoxification
3) Addiction Severity Index (ASI)
4) Motivational Interviewing (MI)
5) Promoting Awareness of Motivational Incentives (PAMI)
Partnerships Are Essential In Advancing the Science of Addiction and in Translating Promising Strategies into Practice

NIDA’s Networking Initiative

Priority Areas for NIDA

- Prevention Research (Children and Adolescents)
  - genetics
  - development
  - environment
  - co-morbidity
- Treatment Interventions (New Targets)
- HIV/AIDS Research
- Translating Research into Practice
We Need Addiction Medicine to…

Continue to Study
Drug Abuse & Addiction
at All Levels and to Help
Ensure that Promising
Strategies Are Adopted
in Clinical Practice

Where Do We Need
to Go From Here?

We Need to Work
TOGETHER to…

Advance the SCIENCE

and to…

Erase the STIGMA

Visit Our Website @

www.drugabuse.gov
Addiction is the Quintessential Biobehavioral Disorder