Tobacco Research at NIDA: Basic Science, Prevention, Treatment and Regulatory Science

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Susan Weiss, PhD
Director
Division of Extramural Research
NIDA FY 2014 Tobacco Grants (294, $101M)*

* Does NOT include FDA/CTP supported grants and contracts
Addiction and Other Psychiatric Diseases Involve Multiple Factors

Brain Mechanisms

Biology - Genes/Development

Environment

DRUG

Addiction

[Image of a family tree and a panoramic view of a landscape]
Themes for NIDA Research

• Basic Science
  ✓ Genetics (understanding impact of genetics on vulnerability to smoking-related morbidity/mortality)
  ✓ Biomarkers of vulnerability
• New Delivery Systems (ENDS)
• Medications Development
• Behavioral and Integrated Treatments
• Vulnerable Populations (e.g., youth, pregnant women, mental illness)
• Prevention (ABCD)
• Integrated Tobacco Surveillance and Regulatory Studies (MTF, PATH, and others)
Convergent Results Support CHRNA5/A3/B4 Gene Cluster Association with Nicotine Dependence

\[ \text{a}5, \text{a}3, \beta4, \text{have a high concentration in habenula and interpeduncular nucleus} \]

Novel genes identified in a high-density genome wide association study for nicotine dependence

The CHRNA5/A3/B4 Gene Cluster Variability as an Important Determinant of Early Alcohol and Tobacco Initiation in Young Adults

\[ \text{Medial habenula} \]

\[ \alpha-5/\alpha-3 \text{ nicotinic receptor subunit alleles increase risk for heavy smoking} \]
Genes Affect Risk for Smoking Progression, Odds of Quitting and Whether Medications May Help

Polygenic Risk and the Developmental Progression to Heavy, Persistent Smoking and Nicotine Dependence

Pharmacotherapy effects on smoking cessation vary with nicotine metabolism gene (CYP2A6)


More Youth in USA Using E-Cigarettes Than Tobacco Cigs

Past Month Use of E-Cigs vs. Traditional Cigarettes in the 2014 Monitoring the Future Study of 8th, 10th and 12th Grade Students in USA

Monitoring the Future Study, University of Michigan
Current Trends and Statistics

- **Who is using e-cigarettes?**
  - Use doubling every year since 2010
  - High school kids use e-cigarettes more often than combustible cigarettes in the last 30 days (MTF and NYTS)
    - 25-55% of kids that used e-cigarettes in past 30d had *never used combustibles* (MTF)
  - In adults, dual use with combustibles most common scenario
    - Is this temporary until e-cigarettes routinely deliver combustible levels of nicotine?
    - Regular vapers who quit combustibles generally use higher power devices likely to deliver highest levels of nicotine

![Bar chart showing e-cigarette use by grade level (8th, 10th, 12th) and type (E-Cigs Only, E-Cigs and Any Lifetime Tobacco).](image)
E-Cigarette Aerosol Contents

- **Long-term safety of aerosol inhalation is unknown**
  - Many constituents are “Generally Recognized as Safe” (GRAS) for food, **BUT** lung inhalation bypasses first pass metabolism
  - Some compounds same as in tobacco smoke: acrolein, formaldehyde
  - Generally substantially lower toxin levels (9-450x) than in tobacco smoke

- **Variable voltage devices can alter the aerosol**
  - Higher voltage produces higher temps, more nicotine in aerosol
  - This may also increase levels of toxic compounds: e.g., formaldehyde
  - Under certain conditions, levels near those of conventional cigarettes

- **E-cigarette aerosol is less complex than tobacco smoke**
  - ≈ 5000 compounds in tobacco smoke
  - ≈ 70 known carcinogens in tobacco smoke
  - Many fewer compounds in e-cigarette aerosol

Source: Goniewicz et al, 2014; Kosmider et al, 2014
E-Cigarettes and Policy Implications (Federal, State, Local Level)

- **2009 Family Smoking Prevention and Tobacco Act (Tobacco Control Act)**
  - FDA currently regulates cigarettes, cigarette tobacco, roll-your-own tobacco and smokeless tobacco products (e.g., limits sale, distribution, advertising, establishes product standards)
  - Newly proposed (2014) regulations include e-cigarettes, cigars, pipe tobacco and some dissolvables; final rule expected June 2015 (*still waiting*)

- **E-cigarette regulatory action mostly taking place on the State and local-level**
  - ~41 States restrict sale of e-cigarettes to minors; 18 states have laws regulating use (e.g., in state buildings, schools, public places/transport)
  - Local laws on e-cigarette parallel combustible tobacco product regulations
    - e.g., Montgomery (MD) County Council voted to ban e-cigarette (e-hookah, e-pipe and vape pens) use in public places and increase taxes on products

- **Currently minimally regulated**
  - Over 250 e-cigarette brands in U.S.; thousands of e-juice flavors
Most Common Research Areas

- How are devices being used/dual use (Eissenberg)
- Abuse liability (Rose)
- Nicotine delivery characteristics (George)
- Role of flavors (Krishnan-Sarin)
- User perceptions/advertising (O’Connor)
- Safety of constituents (Talbot)
- Natural history studies of use (Carpenter)
- Animal/in vitro models (Robinson)

Current NIH E-Cigarette Funding, FY15

<table>
<thead>
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<th></th>
<th>NIDA</th>
<th>NCI</th>
<th>NHLBI</th>
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<tr>
<td>Total Grants</td>
<td>19</td>
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<td>NIH/IC</td>
<td>4</td>
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<td>Total $$</td>
<td>$13,623,174</td>
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*Additional NIDA: SBIR Contract (NJOY) - $330,428; portions of PATH and MTF
Research Questions in Need of Answers

• **Youth use of e-cigarettes relative to combustible**
  – Role in long term e-cigarette use and/or nicotine addiction
  – Which products most common for initiation?
  – Are e-cigarettes a gateway to combustible?

• **Prevalence of alternative drug use in e-cigarettes**
  – E-cigarette cartomizers filled with marijuana extracts are a standard medicinal marijuana product
  – Use of other substances routinely mentioned in blogs/chat rooms

• **What is the addictive potential of e-cigarettes?**

• **Need to determine role in cessation and harm reduction**
  – Useful tool for nicotine cessation?
  – What are real risks and benefits versus combustible?
  – Likelihood of initiation/addiction by adults?
  – Role for special populations such as schizophrenia, heavy smokers
Therapies for Smoking Cessation

- 7 FDA approved first-line pharmacotherapies:
  - 5 NRT and 2 non-NRT

- Cessation treatment has limited efficacy after 6 months
  Only 20% using pharmacotherapy are abstinent for more than a year.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Abstinence Rate at 6 mo, %</th>
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<tbody>
<tr>
<td>Self-help and Quitline</td>
<td>8.5% and 12.7%</td>
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<tr>
<td>Counseling alone</td>
<td>14.6%</td>
</tr>
<tr>
<td>* Varenicline (2mg/day and 1 mg/day)</td>
<td>33.2% and 25.4%</td>
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<tr>
<td>* Bupropion SR</td>
<td>24.2%</td>
</tr>
<tr>
<td>* Nicotine patch</td>
<td>23.4%</td>
</tr>
<tr>
<td>Medication and counseling</td>
<td>27.6%</td>
</tr>
</tbody>
</table>

Source: * Treating Tobacco Dependence in Light of the 2008 US Department of Health and Human Services Clinical Practice Guideline
Varenicline & Bupropion SR Combination Therapy for Smoking Cessation

Source: Rose and Behm Am J Psych 2014;171:1199
Immunotherapies for Addiction Treatment (i.e., Vaccines)

Antibodies Can Reduce Brain Concentrations

Targeting the drugs, not the receptors
Mindfulness Meditation for Smoking Cessation

- Individuals received
  - integrative-body-mind training, a form of mindfulness meditation
  - generalized relaxation training
- IBMT reported reductions in smoking, withdrawal symptoms and cravings for cigarettes
- Positively associated with activity in brain areas associated with self-control and decision-making

Source: Tang et al PNAS 2013;110:13971
Comorbid Disorders

Mental Disorder

Addictive Disorder

COMORBIDITY

Smoking Epidemiology

Non-Ill Population:
- Alcoholism: 23%*
- Drug Addictions: 56.1% (current); 43.5% (lifetime)**
- Schizophrenia: 67.9% (current); 49% (lifetime)**
- Depression: 70-85%***
- Anxiety: 44.7% (current); 36.6% (lifetime)**
- PTSD: 54.6% (current); 46% (lifetime)**
- ADHD: 44.6% (current); 45.3% (lifetime)**
- 41-42% (adults)****
- 19-46% (adolescents)****

Maintenance pharmacotherapy + CBT can help individuals with Serious Mental Illness stay smoke-free.

Maintenance pharmacotherapy with varenicline and cognitive behavioral therapy improved prolonged tobacco abstinence rates for individuals with serious mental illness after 1 year of treatment and at 6 months after treatment discontinuation.

Source: *Evins et al., Maintenance Treatment with Varenicline for Smoking Cessation in Patients with SCZ and Bipolar Disorder, JAMA 311: 143-54, 2014*
Reduced-Nicotine Cigarettes — A Promising Regulatory Pathway

Michael Fiore, M.D., M.P.H., M.B.A., and Timothy Baker, Ph.D.


Perspective:
Reduced-Nicotine Cigarettes — A Promising Regulatory Pathway
Michael Fiore, M.D., M.P.H., M.B.A., and Timothy Baker, Ph.D.

Regulatory Science: Randomized Trial of Reduced-Nicotine Standards for Cigarettes

Source: Donny et al 2015 NEJM 373(14):1340
Population Assessment of Tobacco and Health (PATH) Study

- National, longitudinal cohort study of ~46,000 users of tobacco products and those at risk for tobacco use ages 12 and older in the U.S.
- Funded by the Center for Tobacco Products, FDA.
- Results from this study will help inform the impact of FDA regulatory authority over tobacco products, and help to inform future activities.
PATH Study Domains *(examples)*

- Baseline Sample 45,971 total (32,320 age 18+; 13,651 age 12-17)

- Outcomes
  - Tobacco Product Use including Dual Use, Switching, New Products
  - Tobacco Use Behaviors including Initiation, Cessation/Quitting, Relapse
  - Health Outcomes

- Mediators/Moderators
  - Demographics
  - Knowledge, Attitudes, Beliefs, and Risk Perceptions
  - Tobacco Addiction
  - Peer, Environmental, Contextual influences
  - Mental Health/Substance Abuse Co-morbidities
PATH Next Steps

• Data collection ongoing
• Selected analysis ongoing
• Accelerated efforts to have the PATH Study be a resource to the scientific community while ensuring highest data quality
• More Information: PATHstudyinfo.nih.gov
Adolescent Brain Cognitive Development (ABCD): A Longitudinal Study

Ten year longitudinal study of 10,000 children from age 10 to 20 years to assess effects of substances on individual brain development trajectories
Adolescence is the period of greatest vulnerability for Substance Abuse & Addiction

Source: NIAAA National Epidemiologic Survey on Alcohol and Related Conditions, 2003
Adolescent Brains Are Still Developing

Frontal Brain Connections are Among the Latest to Mature

Brain areas where volumes are smaller in adolescents than young adults


During Adolescence the COGNITION EMOTION Connection is Still under Development

Increasing Evidence that Early Cannabis Use Alters Brain Structure: Cannabis Decreases Axonal Fiber Connectivity

Axonal paths with reduced connectivity (measured with diffusion-weighted MRI) in cannabis users (n=59) than in controls (N=33).

Source: Zalesky et al Brain 2012.
Adverse Psychiatric/Education/Social Outcomes as a Function of Frequency Of Cannabis Use Before Age 17 (at age 30; n=2500-3700)

Consistent and dose-response associations were found between frequency of adolescent cannabis use and adverse outcomes

Source: Silins E et al., The Lancet September 2014.
Ten year longitudinal study of 10,000 children from age 10 to 20 years to map individual trajectories of human brain development and to evaluate how it is influenced by genetics and environment, most notable drugs (including nicotine, marijuana, and alcohol), and by mental illnesses.
Central Research Questions

• What is the impact of diverse patterns of use of marijuana, alcohol, nicotine and other substances on the structure and function of the developing brain, as revealed by brain imaging?
• What are the consequences of substance use on physical health, psychosocial development, information processing, learning, memory, academic achievement, motivation, emotion regulation, and other behaviors?
• How does substance use affect the expression of psychopathology, including substance use disorders, and how does the emergence of psychopathology influence drug use?
• What factors (prenatal, genetic, epigenetic, neurobiological, psychosocial, family history, head trauma, others) influence substance use and its consequences during development?
• In what way does use of each substance contribute to the use of others (gateway interactions)?
Timeline:
1) Biennial Imaging; 2) Annual In-person assessments; 3) Semi-annual or Quarterly web-based surveys

Measures: Substance use, Cognition, Emotion, Mental Health, Physical health, Executive Function, General Intelligence, Environment, Biospecimens: Genetics, Epigenetics
All Drugs Abused by Humans Raise Brain Dopamine Levels in the Nucleus Accumbens

Source: Nestler, Nature Neurosci, 2005

**METHAMPHETAMINE**
- Dose (mg/kg IV)
- 5
- 2.5
- 1

0 0 20 40 60 80 min

**NICOTINE**
- Dose (mg/kg sc)
- 0.6

0 1 2 3 hr

Source: Di Chiara et al.

Source: Nestler, Nature Neurosci, 2005
DA and Drug Reinforcement and Age Effects

DA increases are associated with drug rewarding effects and decrease with age.
DOPAMINE D$_2$ RECEPTORS
Decrease with Age in the Human Brain

Source: GENSAT
Gene Variants and Nicotine Dependence

CHRNA5/A3/B4

CYP2A6

Source: TAG Nature Genetics 2010;42(5):441

Habenula and Negative Reward

**Habenula neurons** increased firing for NO REWARD and decreased firing for REWARD

**Dopamine neurons** increased firing for REWARD and decreased firing for NO REWARD.


Habenula inhibits dopamine neurons
Habenula communicates negative reward signals to dopamine neurons
E-cigarette Activities at NIDA

- Types of research grants or contracts (including supplements)

<table>
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<th>P50</th>
<th>R21</th>
<th>K01</th>
<th>Supplements</th>
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<td>3</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td>5</td>
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- Funding source (of the e-cig component)
  - FDA: 19
  - IC: 12

- Major focus of research topic from IC perspective
  - Content & safety of e-liquid and aerosol
  - Nicotine PK
  - Abuse Liability
  - How are devices used

- Type of study
  - Animal research: 2
  - Clinical research: 20
  - Cellular research: 4
  - Cohort/epidemiology: 2

- Other activities
  - Development of standardized research e-cigarette
  - Large Surveys of tobacco product use including ecigs
    - Monitoring the Future (MTF)
    - Population Assessment of Tobacco and Health (PATH)
Although Adolescents are in their Prime Physically, Morbidity and Mortality Doubles As A Result of Behavioral Changes that Occur During the Transition from Childhood to Adolescence

What Makes This Time One of Increased Risk?
Types of Electronic Nicotine Devices

1. Disposable e-cigarette
   - NJOY, White Cloud, Greensmoke

2. Rechargeable e-cigarette
   - Markten, Mistic, blu, VUSE

3. Pen-style, medium-sized rechargeable e-cigarette
   - eGo, Totally Wicked

4. Tank-style, large-sized rechargeable e-cigarette
   - Volcano Lavatube

Sealed device or cartridge

User adds liquid to device

Source: Grana, et al, 2014
Gateway Effects of Nicotine?

Days of Cocaine Exposure

Chronic Nicotine Before Cocaine
Chronic Cocaine Only

Chronic, compulsive
Acute, controlled

Pattern of Drug Taking

Epigenetic Changes: Wide Ranging Impact