2017-18 Lecture Series

A Look at Some Old and Not So Old Drugs: COCAINE
Cocaine-- 2018

- Lifetime >1000 Peer Reviewed Articles, Chapters, Texts- [www.pubmed.com](http://www.pubmed.com)
- Recent Awards : ASAM Annual McGovern Award & Prize and PATH Lifetime Achievement Awards
- Mark S. Gold, MD
  17th UFAA Distinguished Professor Chairman, Professor, Dizney Distinguished Professor, Eminent Scholar, Emeritus Eminent Scholar (1990-2015)
- Adjunct Professor, Washington University School of Medicine, St. Louis, Missouri
- Chairman, RiverMend Health Scientific Advisory Boards; Editor: [www.addictionresearchyoucanuse.com](http://www.addictionresearchyoucanuse.com)

DEA---2/21/18
Most Cited MSG Articles

• **Citation Classics:**
  1. New concepts in cocaine addiction: the dopamine depletion hypothesis
     - CA Dackis, MS Gold - Neuroscience & Biobehavioral Reviews, 1985 - Elsevier
  2. Opiate withdrawal using clonidine: a safe, effective, and rapid nonopiate treatment
     - MS Gold, AC Pottash, DR Sweeney, HD Kleber - Jama, 1980 - jama.jamanetwork.com
  3. Problematic internet use: proposed classification and diagnostic criteria
     - ..., ST Szabo, M Lazoritz, MS Gold - Depression and ..., 2003 - Wiley Online Library
  4. Noradrenergic hyperactivity in opiate withdrawal supported by clonidine reversal of opiate withdrawal.
     - MS Gold, DE Redmond, HD Kleber - The American journal of ..., 1979 - psycnet.apa.org
  5. Neurobiology of food addiction
     - DM Blumenthal, MS Gold - Current Opinion in Clinical Nutrition & ..., 2010 - journals.lww.com
     - MS Gold - Psychiatric Clinics of North America, 1993 - psycnet.apa.org

• **High Citation Recognition:**
  1. Hypothyroidism and depression: evidence from complete thyroid function evaluation
  2. Comorbid cigarette and alcohol addiction: epidemiology and treatment
     - NS Miller, MS Gold - Journal of addictive diseases, 1998 - Taylor & Francis
  3. Cocaine abuse: Neurochemistry, phenomenology, and treatment
     - MS Gold, AM, Washton, CA Dackis - Cocaine use in America: ..., 1985 - books.google.com
  4. Methamphetamine causes microglial activation in the brains of human abusers
     - ..., H Matsuzaki, T Ueki, N Mori, MS Gold - The Journal of ..., 2008 - Soc Neuroscience
  5. Body mass index and alcohol use
     - KD Kleiner, MS Gold, K Frostpineda - Journal of addictive ..., 2004 - Taylor & Francis
  6. Setting the standard for recovery: Physicians' Health Programs
     - ..., AT McLellan, WL White, LJ Merlo, MS Gold - Journal of Substance ..., 2009 - Elsevier
Leah-Perle Bloomenstein, DEA

Leah-Perle Bloomenstein is an Intelligence Research Specialist (IRS) with the Drug Enforcement Administration (DEA). IRS Bloomenstein is currently assigned to DEA's Domestic Strategic Intelligence Unit at DEA Headquarters. The Domestic Strategic Intelligence Unit provides senior DEA officials and other U.S. government policy makers with high-priority strategic intelligence analyses on the drug trade in the United States and assesses the changing dynamics of counterdrug situation across the country.

IRS Bloomenstein is a 2008 graduate of Wheaton College where she earned a Bachelor of Arts degree in Russian Studies and International Relations. After college, IRS Bloomenstein attended the University of Durham in Durham, England and earned a Masters of Art in International Studies in 2013. After a period in the private sector, where she gained valuable import and export experience, IRS Bloomenstein joined DEA in 2017 and currently focuses on domestic cocaine trends.

Leah Bloomenstein, DEA (Domestic Intel), *Current Intelligence on Cocaine*
• CBP New York City @CBPNewYorkCity
• This passenger was 'busted' out of his pants by @CustomsBorder #JFK with an estimated $164,000 of Cocaine

• Colombia’s coca boom & American cocaine use
Submarines & Semi-Submersibles used for cocaine smuggling
2017- Cocaine Production, Use, Deaths Increasing

Cocaine Production

New Cocaine Users in the USA

Colombia’s coca boom
Coca cultivation is on the rise in Colombia.

New cocaine users in U.S.
The number of people trying cocaine in the U.S. has increased.

Figures are in hectares, an area equal to about 2.5 acres of land

Source: State Department
WASHINGTON POST

Source: U.S. Substance Abuse and Mental Health Services Administration
WASHINGTON POST
Jean Lud Cadet, M.D.

Jean Lud Cadet, M.D. came to NYC from Haiti in 1970. He attended Columbia University College of Physicians and Surgeons from which he obtained his MD in 1979. He did residency training in Psychiatry at the Department of Psychiatry at Columbia University and in Neurology at the Department of Neurology at Mount Sinai Medical Center, both in New York City. He came to NIDA, IRP in 1992 where he is presently a senior NIH investigator and the Chief of the Molecular Neuropsychiatry Research Branch. Dr. Cadet has co-authored more than 300 papers, abstracts and book chapters on the molecular neurobiology of addiction and neurodegeneration. He has also written about cognitive deficits in cocaine and marijuana abusers. Presently, his laboratory studies the molecular mechanisms of stimulant-induced changes in the expression of genes and proteins in specific neuronal cells. He is also investigating the epigenetic bases of methamphetamine and oxycodone addiction.

Senior Investigator (tenured)
Chief, Molecular Neuropsychiatry Research Branch
Chief, Molecular Neuropsychiatry Section
National Institutes of Health (NIH)/National Institute on Drug Abuse (NIDA) Intramural Research Program
Baltimore, MD

Jean Lud Cadet, MD, National Institute on Drug Abuse (NIDA)

*Cocaine, Methamphetamines, and Psychostimulants: Changes the Brain and Damages It*
Jean Lud Cadet, M.D. -- Drugs may cause changes that are quite irreversible and cause the abstinent patient to appear as if they have a psychiatric disease.
Thomas R. Kosten, MD

- JH Waggoner Chair and Professor of Psychiatry, Neuroscience, Pharmacology, Immunology & Pathology
- Director, Institute for Clinical and Translational Research
  Baylor College of Medicine

EDUCATION
- MA from Yale University
  01/1995 - New Haven, Connecticut, United States
- Clinical Fellowship at Yale University School of Medicine
  01/1983 - New Haven, Connecticut, United States
- M.D. from Cornell University Medical College
  01/1977 - New York, NY, United States
- BS from Rensselaer Polytechnic Institute
  01/1973 - Troy, New York, United States
- Residency at Yale University School of Medicine
  01/1981 - New Haven, Connecticut, United States
WHAT about Treatments for Cocaine Users—like we have for Opioids (O.D., Detox., Relapse Prevention)?
The American Disease
Origins of Narcotic Control
Expanded Edition
David F. Musto, M.D.

The American Disease
Oxford University Press
Life Expectancy Drops Again As Opioid Deaths Surge In U.S.

• Some researchers studying mortality trends say the opioid epidemic is just part of a larger problem.

• "It's also a crisis in which people are killing themselves in much larger numbers — whites especially," says Anne Case, an economist at Princeton University who has been studying what she and her husband and fellow Princeton economist Angus Deaton call "Deaths of Despair."

• "Deaths from alcohol have been rising as well. So we think of it all being signs that something is really wrong and whatever it is that's really wrong is happening nationwide," Case says.

• The decline of well-paying jobs with significant yearly salary increases, job security and good benefits may be fueling a sense of frustration and hopelessness, Case says. That may be one reason fewer people are getting married and more people are having children outside of marriages, Case says.

• "They don't have a good job. They don't have a marriage that supports them. They may have children that they do or don't see," Case says. "They have a much more fragile existence than they would have had a generation ago."

• As a result, "it may be the deaths from drugs, from suicide, from alcohol are related to the fact that people don't have the stability and a hope for the future that they might have had in the past," Case says.
Drug Deaths in the USA---Cocaine is #2

Top 10 Drugs Involved in Overdose Deaths, 2014
- Heroin: 10,863
- Cocaine: 5,856
- Oxycodone: 5,417
- Alprazolam: 4,217
- Fentanyl: 4,200
- Morphine: 4,022
- Methamphetamine: 3,728
- Methadone: 3,495
- Hydrocodone: 3,274
- Diazepam: 1,729

Top 10 Drugs Involved in Overdose Deaths, 2010
- Oxycodone: 5,256
- Methadone: 4,408
- Cocaine: 4,312
- Alprazolam: 3,677
- Heroin: 3,020
- Morphine: 2,941
- Hydrocodone: 2,844
- Fentanyl: 1,645
- Diazepam: 1,448
- Methamphetamine: 1,388
NOTES: Deaths are classified using the International Classification of Diseases, Tenth Revision. Drug-poisoning deaths are identified using underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Drug overdose deaths involving selected drug categories are identified by specific multiple-cause-of-death codes: heroin, T40.1; natural and semisynthetic opioids, T40.2; methadone, T40.3; synthetic opioids other than methadone, T40.4; cocaine, T40.5. Deaths involving more than one drug (e.g., a death involving both heroine and cocaine) are counted in both categories. The percentage of drug overdose deaths that identified the specific drugs involved varied by year ranging from 75-79% from 1999 through 2013 and from 81-85% from 2014 through 2016.

Age-adjusted rates for drug overdose deaths involving cocaine
United States, 1999-2016

NOTES: Deaths are classified using the International Classification of Diseases, Tenth Revision. Drug-poisoning deaths involving cocaine are identified using underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14 and multiple-cause-of-death code T40.5. The percentage of drug overdose deaths that identified the specific drugs involved varied by year ranging from 75-79% from 1999 through 2013 and from 81-85% from 2014 through 2016.
State of Florida Fentanyl-Related Deaths (N=1391)
Bruce Goldberger, Ph.D.

Top 10 Co-occurring Substances among Fentanyl-Caused Deaths in 2016

<table>
<thead>
<tr>
<th>Substance</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Cocaine</td>
<td>46.3%</td>
</tr>
<tr>
<td>Morphine</td>
<td>37.0%</td>
</tr>
<tr>
<td>Heroin</td>
<td>26.9%</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>25.1%</td>
</tr>
<tr>
<td>Ethanol</td>
<td>23.9%</td>
</tr>
<tr>
<td>Fentanyl_Analogs</td>
<td>20.9%</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>18.8%</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>13.5%</td>
</tr>
<tr>
<td>Codeine</td>
<td>10.2%</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>7.0%</td>
</tr>
</tbody>
</table>
Deaths with Fentanyl Analog in 2016

Deaths with Fentanyl Analog per 100,000 Population

Deaths with Fentanyl Analog

<table>
<thead>
<tr>
<th>Cause</th>
<th>Present</th>
<th>Grand Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>In Combination with Other Drugs</td>
<td>871</td>
<td>931</td>
</tr>
<tr>
<td>Only</td>
<td>94</td>
<td>95</td>
</tr>
<tr>
<td>Grand Total</td>
<td>965</td>
<td>1,026</td>
</tr>
</tbody>
</table>

Cause or Present?

<table>
<thead>
<tr>
<th>Age Group</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;18</td>
</tr>
<tr>
<td>Deaths</td>
<td>1</td>
</tr>
<tr>
<td>% of Total</td>
<td>0.10%</td>
</tr>
</tbody>
</table>

Manner of Death

<table>
<thead>
<tr>
<th>Manner of Death</th>
<th>Deaths</th>
<th>% of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accidental</td>
<td>1,014</td>
<td>98.83%</td>
</tr>
<tr>
<td>Suicide</td>
<td>7</td>
<td>0.68%</td>
</tr>
<tr>
<td>Homicide</td>
<td>3</td>
<td>0.29%</td>
</tr>
<tr>
<td>Natural</td>
<td>1</td>
<td>0.10%</td>
</tr>
<tr>
<td>Undetermined</td>
<td>1</td>
<td>0.10%</td>
</tr>
</tbody>
</table>

Top 10 Co-occurring Substances among Fentanyl Analog-Caused Deaths (N=965)

<table>
<thead>
<tr>
<th>Substance</th>
<th>Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine</td>
<td>457 (47.4%)</td>
</tr>
<tr>
<td>Morphine</td>
<td>329 (34.1%)</td>
</tr>
<tr>
<td>Ethanol</td>
<td>266 (27.5%)</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>265 (27.5%)</td>
</tr>
<tr>
<td>Heroin</td>
<td>215 (22.3%)</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>202 (20.9%)</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>191 (19.8%)</td>
</tr>
<tr>
<td>Codeine</td>
<td>113 (11.7%)</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>112 (11.6%)</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>68 (7.0%)</td>
</tr>
</tbody>
</table>

Frequency of Fentanyl Analog Occurrences (N=1,274)

<table>
<thead>
<tr>
<th>Substance</th>
<th>Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carfentanil</td>
<td>552 (43.3%)</td>
</tr>
<tr>
<td>Furanyl fentanyl</td>
<td>287 (22.5%)</td>
</tr>
<tr>
<td>Despropionyl fentanyl (4-ANPP)</td>
<td>179 (14.1%)</td>
</tr>
<tr>
<td>Acetyl fentanyl</td>
<td>133 (10.4%)</td>
</tr>
<tr>
<td>Fluorobutyryl / Fluoroisobutyryl fentanyl</td>
<td>73 (5.7%)</td>
</tr>
<tr>
<td>Despropionyl fluorofentanyl</td>
<td>21 (1.6%)</td>
</tr>
<tr>
<td>Butyryl fentanyl / Isobutyryl fentanyl</td>
<td>16 (1.3%)</td>
</tr>
<tr>
<td>Fluorofentanyl</td>
<td>9 (0.7%)</td>
</tr>
<tr>
<td>Beta-hydroxythiofentanyl</td>
<td>4 (0.3%)</td>
</tr>
</tbody>
</table>

Florida drug-Related Outcomes Surveillance and Tracking (FROST) System

http://frost.med.ufl.edu/

Funding provided by BJA, DOJ
Seized Cocaine Containing Fentanyl, Carfentanil

• The widespread seizures of contaminated cocaine indicate that drug dealers are commonly mixing fentanyl and fentanyl-related substances into the drug.

• In some cases, this is done purposefully to increase the drug’s potency or profitability. In other cases, fentanyl is inadvertently mixed into cocaine by drug dealers using the same blending equipment to cut various types of drugs, such as heroin.

• Regardless, the adulteration often occurs without the users’ awareness, which leads to overdose incidents. Individuals who use cocaine occasionally are at an extremely high risk of overdose.
Recent Increases in Cocaine-Related Overdose Deaths and the Role of Opioids

• Objectives. To assess trends in cocaine overdose deaths and examine the role opioids play in these deaths.

• Methods. We used data on drug overdose deaths in the United States from 2000 to 2015 collected in the National Vital Statistics System to calculate annual rates and numbers of cocaine-related overdose deaths overall and deaths both involving and not involving opioids. We assessed statistically significant changes in trends with joinpoint regression.

• Results. Rates of cocaine-related overdose deaths increased significantly from 1.26 to 2.50 per 100 000 population from 2000 to 2006, declined to 1.35 in 2010, and increased to 2.13 in 2015. Cocaine-related overdose deaths involving opioids increased from 0.37 to 0.91 from 2000 to 2006, declined to 0.57 in 2010, and then increased to 1.36 in 2015. Cocaine-related overdose deaths not involving opioids increased from 0.89 to 1.59 from 2000 to 2006 and then declined to 0.78 in 2015.

Conclusions. Opioids, primarily heroin and synthetic opioids, have been driving the recent increase in cocaine-related overdose deaths. This corresponds to the growing supply and use of heroin and illicitly manufactured fentanyl in the United States.

• Cocaine-related overdose deaths increased significantly between 2000 and 2006. Between 2006 and 2010, consistent with a reduction in supply and an increase in street prices. The public health and public safety response to increasing cocaine-related overdose deaths should be comprehensive and informed by the role opioids play. This is particularly important given the rapid increase in cocaine-related deaths involving synthetic opioids such as fentanyl and its highly potent analogs.

Adulterants--- Poisonings

• "The large majority (87%) of cocaine bricks contained levamisole and/or levamisole mixtures with dexamisole, while only one percent of bricks contained various other cutting agents"

• page 84  DEA 2017 National Drug Threat Assessment

• https://www.dea.gov/docs/DIR-040-17_2017-NDTA.pdf
Of the nation’s 10 leading causes of death, significant increases last year came in unintentional injuries (which include drug overdoses), Alzheimer’s disease and suicides.

(2017- CDC National Center for Health Statistics)
Missed opportunities: Opioid overdoses and suicide

Publish date: August 29, 2017
By A. Benjamin Srivastava, MD  Mark S. Gold, MD

..more than 50% of patients with opioid use disorder have histories of major depressive disorder, which, when untreated, may further drive suicidal thoughts and behavior.10,11 Maria A. Oquendo, MD, PHD, immediate past president of the American Psychiatric Association, wrote in a guest post on the blog of Nora D. Volkow, MD, director of the National Institute on Drug Abuse, about the strong link between opioid use disorders and suicidal thoughts and behavior. Furthermore, a 2004 literature review on substance use disorders and suicide found that individuals with opioid use disorders had a 13 times greater risk of completed suicide, compared with the general population.12

Additional associations

A recent study of nearly 5 million veterans enrolled in the Veterans Health Administration demonstrated that, even when adjusted for age and comorbid psychiatric diagnoses, opioid use disorder was associated with an increased risk for suicide; particularly striking was that this risk was doubled in women.13

A survey of 40,000 subjects from the 2014 National Survey on Drug Use and Health demonstrated that prescription opioid misuse was associated with an increased risk of suicidal ideation, and weekly misuse was associated with increased suicide planning and attempts.
Leah-Perle Bloomenstein
Intelligence Research Specialist
Domestic Strategic Intelligence Unit
DEA

Current Intelligence on Cocaine
Cocaine Trends

Drug Enforcement Administration
Strategic Intelligence Section
Domestic Strategic Intelligence Unit
Leah-Perle Bloomenstein
Overview

- Colombia
  - Record production
  - Increased domestic availability
- Southwest border seizures
- National-level survey, treatment, and death data
Cocaine Cultivation and Production

Source: U.S. Government Estimates

Coca Cultivation (Hectares) - Potential Cocaine Production (Metric Tons)
Colombia Potential Cocaine Production and Territorial Seizures

Source: USG estimates, Colombian Observatory on Drugs

Metric Tons

- Pure
- Export Quality
- Territorial Seizures

UNCLASSIFIED
Cocaine Flow

Source: U.S. Government Database of Drugs Seizures and Movement
Southwest Border Seizures
Total Kilograms Seized FY 2012 to FY 2017

Source: CBP
Price and Purity Converging

Source: DEA
National-Level Use, Availability, Treatment, and Death Data
2017 NDTS Greatest Drug Threat

Source: DEA
Law Enforcement Perceptions of Cocaine as the Greatest Drug Threat 2017

Source: DEA National Drug Threat Survey
National Forensic Laboratory System

Cocaine

Source: NFLIS
U.S. Past Year Cocaine Initiates and Current Users

- Stabilized use rates
- 0.7% of the U.S. population

Source: National Survey on Drug Use and Health (NSDUH)
U.S. Past Year Cocaine Initiates and Colombia Potential Cocaine Production

Source: USG estimates, National Survey on Drug Use and Health (NSDUH)
National Treatment Admissions

Source: TEDS
U.S. Cocaine Poisoning Deaths

Source: USG estimates, Centers for Disease Control (CDC)

Overdose deaths, 63,632

Involving cocaine, 10,375

Source: USG estimates, Centers for Disease Control (CDC)
Cocaine and Fentanyl

2016 Cocaine & Synthetic Opioids
Top States for Overdose Deaths
Per 100,000 Population

Source: CDC/Wonder
Thank you. Questions?

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Jean Lud Cadet, M.D.
Senior Investigator & Chief,
Molecular Neuropsychiatry Research Branch,
NIDA Intramural Research Program

Cocaine Changes the Brain and Damages It
Pathobiology of Psychostimulants: Cocaine and METH

Jean Lud Cadet, M.D.

Molecular Neuropsychiatry Research Branch
Presentation Outline

- Dopamine systems
- Cocaine
- Cocaine and DA systems
- CUD and neuropsychiatry
- CUD and cognitive findings
- CUD and neuroimaging findings
- Basic mechanisms of CUD complications
- Summary and suggestions
Presentation Outline

- Dopamine systems
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- Summary and suggestions
Transmitters contained in projecting pathways in the brain

<table>
<thead>
<tr>
<th>Neurotransmitters</th>
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<tbody>
<tr>
<td><strong>Monoamines</strong></td>
</tr>
<tr>
<td><strong>Catecholamines</strong></td>
</tr>
<tr>
<td>Dopamine</td>
</tr>
<tr>
<td>Norepinephrine</td>
</tr>
<tr>
<td>Epinephrine</td>
</tr>
<tr>
<td><strong>Indoleamine</strong></td>
</tr>
<tr>
<td>Serotonin</td>
</tr>
<tr>
<td><strong>Neuropeptides</strong></td>
</tr>
<tr>
<td>Oxytocin</td>
</tr>
<tr>
<td>Orexins (Hypocretins)</td>
</tr>
<tr>
<td>Crh</td>
</tr>
<tr>
<td>Vasopressin</td>
</tr>
</tbody>
</table>
Dopamine

Functions in modulating attention, reward, pleasure, motor control.
Dopamine Neurons in the Brain

- **Mesostriatal DA System**
  - Cell bodies in the substantia nigra
  - Terminals in the caudate nucleus and putamen

- **Mesolimbic DA System**
  - Cell bodies in the ventral tegmental area (VTA)
  - Terminals in the olfactory tubercle and nucleus accumbens

- **Mesocortical DA System**
  - Cell bodies in the VTA
  - Terminals in the medial prefrontal and cingulate cortex

- **Tuberoinfundibular DA System**
  - Cell bodies in the hypothalamus
  - Terminals in the pituitary
Presentation Outline

• Dopamine systems
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Basic Facts

• Cocaine is an ester of benzoic acid and methylcognine.

• It is a schedule II medication used primarily for topical anesthesia for ENT and dental surgery, due to its local anesthetic and vasoconstrictor properties.

• Cocaine is a local anesthetic with vasoconstrictor properties because it also blocks NE re-uptake.
Presentation Outline

- Dopamine systems
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Cocaine blocks Dopamine Transporter in the Nucleus Accumbens

Effect of Cocaine on Extracellular DA in vivo

Baumann et al., 1994
Dopamine terminals in the brain

 Vesicles

 Dopamine receptors

 Post-synaptic neuron

 Dopamine terminals in the brain

 Dopamine transporter blocked by cocaine

 Synaptic gap

 Dopamine receptors

 Cocaine

 Dopamine terminals in the brain

 Dopamine transporter blocked by cocaine

 Synaptic gap

 Dopamine receptors

 Cocaine

 Dopamine terminals in the brain

 Dopamine transporter blocked by cocaine

 Synaptic gap

 Dopamine receptors

 Cocaine
Neurotransmitter release

• Vesicular monoamine transporter 2 (VMAT2)

• Transports neurotransmitter dopamine, norepinephrine, serotonin
The “DA Hypothesis” of Stimulant Addiction

- **Stimulant Drugs Elevate Synaptic DA via Interactions with DAT Sites in the Brain**
  - Cocaine is a DA reuptake inhibitor
  - METH is a DA releaser

- **Enhanced DA Transmission in Mesolimbic Neurons Mediates Rewarding Effects of Stimulants**
  - Stimulant self-administration in animals
  - “Binge and crash” cycling in humans
Consequences of increased DA in the synapse

- Drug intake
  - Increased DA levels
  - DA Receptor down-regulation
  - Drug washout
  - DA returns to normal levels
  - Less receptors available to fully activate the nerve cell
  - Craving
Presentation Outline

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The Dopaminergic Pathways of the Brain

- Basal Ganglia
- Nigrostriatal Dopamine Pathway
- Mesolimbic Dopamine Pathway
- Substantia Nigra
- Mesocortical Dopamine Pathway
- Hypothalamus
- Tegmentum
- Tubero-infundibular Dopamine Pathway
Cocaine use disorder

Psychiatric Features

• Acute, Brief Flush.

• Euphoria, Excitability, Hypervigilance.

• Anxiety, Agitation.

• Paranoia, Psychosis.
Cocaine use disorder

Neurological Features

• Stereotypy, Bruxism.

• Chorea, Dystonia, Myoclonus.

• Seizures.

• Strokes.

• Coma.
Presentation Outline

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## Cocaine and cognition

<table>
<thead>
<tr>
<th>STUDY</th>
<th>HISTORY OF COCAINE DEPENDENCE</th>
<th>COGNITIVE FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ardila et al. 1991</td>
<td>Adult Chronic users</td>
<td>↓ Verbal memory  ↓ attention</td>
</tr>
<tr>
<td>O’Malley et al. 1992</td>
<td>Adult Chronic users</td>
<td>↓ Verbal memory  ↓ intelligence  ↓ Verbal abilities  ↓ global neuropsychological functioning</td>
</tr>
<tr>
<td>Strickland et al. 1993</td>
<td>Adult Abstinent users</td>
<td>↓ attention  ↓ visual memory  ↑ Psychomotor speed</td>
</tr>
<tr>
<td>Hoff et al. 1996</td>
<td>Adult Abstinent users</td>
<td>↓ spatial memory  ↓ cognitive flexibility  ↓ Psychomotor speed  ↑ verbal abilities  ↔ verbal memory</td>
</tr>
<tr>
<td>Gillen et al. 1998</td>
<td>Adult Abstinent users</td>
<td>↓ visual memory  ↑ visual motor speed</td>
</tr>
<tr>
<td>Robinson et al. 1999</td>
<td>Adult Chronic cocaine users</td>
<td>↑ Psychomotor functioning  ↓ global neuropsychological functioning</td>
</tr>
<tr>
<td>Bolla et al. 1999</td>
<td>Adult Abstinent users</td>
<td>↓ Visuo-perception  ↓ executive function  ↓ Psychomotor speed  ↓ Manual dexterity</td>
</tr>
<tr>
<td>Roselli et al. 2001</td>
<td>Adult Chronic users</td>
<td>↓ memory  ↓ attention  ↓ executive function</td>
</tr>
<tr>
<td>Colzato et al. 2007</td>
<td>Adult recreational users</td>
<td>↓ inhibitory control</td>
</tr>
<tr>
<td>Woicik et al. 2009</td>
<td>Adult Chronic users</td>
<td>↓ Verbal memory  ↓ executive function  ↓ attention</td>
</tr>
</tbody>
</table>
## Cocaine and cognition

<table>
<thead>
<tr>
<th>STUDY</th>
<th>HISTORY OF COCAINE DEPENDENCE</th>
<th>COGNITIVE FINDINGS</th>
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</thead>
<tbody>
<tr>
<td>Aharonovich et al. 2006</td>
<td>Adult Chronic users</td>
<td>↓ attention</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ memory</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ spatial ability</td>
</tr>
<tr>
<td>Kalapatapu et al. 2011</td>
<td>Young Adult Chronic users Old Adult Chronic users</td>
<td>↓ Psychomotor speed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ attention</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ memory</td>
</tr>
<tr>
<td>Madoz-Gúrpide et al. 2011</td>
<td>Adult Chronic users</td>
<td>↓ executive function</td>
</tr>
<tr>
<td>Winhusen et al. 2013</td>
<td>Adult Chronic users</td>
<td>↓ executive function</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ deshinibition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ apathy</td>
</tr>
<tr>
<td>Verdejo-García et al. 2012</td>
<td>Adult Chronic users</td>
<td>↓ executive function</td>
</tr>
<tr>
<td>Soar et al. 2012</td>
<td>Adult Recreational users</td>
<td>↓ executive function</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ attention</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↔ spatial ability</td>
</tr>
<tr>
<td>Vonmoos et al. 2013</td>
<td>Adult Chronic users Adult Recreational users</td>
<td>↓ executive function</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ attention</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ working memory</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ declarative memory</td>
</tr>
</tbody>
</table>
Cocaine and cognitive functions

Chronic heavy cocaine abusers have persistent neurocognitive deficits.

Abusers of higher doses have more neurobehavioral impairments.

These might be direct effects of chronic cocaine abuse.
Presentation Outline

- Dopamine systems
- Cocaine
- Cocaine and DA systems
- CUD and neuropsychiatry
- CUD and cognitive findings
- CUD and neuroimaging findings
- Basic mechanisms of CUD complications
- Summary and suggestions
# Cocaine and neuroimaging

<table>
<thead>
<tr>
<th>STUDY</th>
<th>History of cocaine use</th>
<th>Neuroimaging method</th>
<th>Main Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldstein et al. 2004</td>
<td>Adult Chronic users</td>
<td>(18)FDG PET</td>
<td>↓visual memory, ↓Verbal memory, ↓ executive function, ↓ attention, Cognitive deficits correlated with DLPC and ACC metabolism</td>
</tr>
<tr>
<td>Tucker et al. 2004</td>
<td>Adult Chronic users</td>
<td>SPECT</td>
<td>↓ decision making, ↑ hyperperfusion in cingulate frontal and superior frontal gyrus</td>
</tr>
<tr>
<td>Kübler et al. 2005</td>
<td>Adult Chronic users</td>
<td>fMRI</td>
<td>↓visual memory, ↓Verbal memory, ↓ activation Pre-frontal cortex, ACC and striatum</td>
</tr>
<tr>
<td>Tomasi et al. 2007</td>
<td>Adult Chronic users</td>
<td>fMRI</td>
<td>↓ activation in thalamus and mesencephalon, ↑ activation Frontal/Parietal cortex, ↑ Deactivation in putamen, ACC, parahippocampal gyrus, and amygdala</td>
</tr>
<tr>
<td>STUDY</td>
<td>Cocaine use disorder</td>
<td>Neuroimaging method</td>
<td>Main Findings</td>
</tr>
<tr>
<td>------------------------------</td>
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</tr>
<tr>
<td>Volkow et al. 2010</td>
<td>Adult Chronic users</td>
<td>((18)FDG PET)</td>
<td>↑metabolic activity in NAcc and OFC when inhibit craving</td>
</tr>
<tr>
<td>Hanlon et al. 2010</td>
<td>Adult Chronic users</td>
<td>fMRI</td>
<td>↓sensorimotor abilities  ↓functional laterality in cortical motor areas</td>
</tr>
<tr>
<td>Moeller et al. 2010</td>
<td>Adult Abstinent users</td>
<td>fMRI</td>
<td>↓prefrontal cortex, striatum, and thalamus activation  ↓thalamic activation associated with poor treatment response</td>
</tr>
<tr>
<td>Volkow et al. 2011</td>
<td>Adult Male and Female Chronic users</td>
<td>((18)FDG PET)</td>
<td>↑brain reactivity to cocaine-cues in females  ↓frontal, cingulate and parietal cortices, thalamus and midbrain for females</td>
</tr>
<tr>
<td>Camchong et al. 2011</td>
<td>Adult Chronic users</td>
<td>fMRI</td>
<td>↓ delay rewards  ↓ decision making  ↓ learning  Hyperconnectivity within the ACC network</td>
</tr>
<tr>
<td>Barrós-Loscertales et al. 2011</td>
<td>Adult Chronic users</td>
<td>fMRI</td>
<td>↔inhibitory control  ↓PFC activation</td>
</tr>
</tbody>
</table>
Cocaine, differential cortical thickness and functional connectivity

A. Seeds
- Left Insula
- Right Insula
- Left TP
- Right TP

B. Connectivity maps
- x = 2, y = 32, z = 15
- x = 2, y = 34, z = 20
- x = 0, y = 31, z = 15
- x = -2, y = 34, z = 21

C. Connectivity difference maps
- x = -1, y = -50, z = 23
- x = -4, y = 0, z = 21
- x = -1, y = -50, z = 23
- x = 7, y = -8, z = 15

Legend:
- HC: High Contrast
- CU: Control
- Overlap

Images depict brain regions and connectivity patterns associated with cocaine exposure.
Cocaine dose and frontal connectivity

$R^2 = 0.21 \quad P = 0.00016$
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Cocaine use disorder
Basic Mechanisms

• Psychiatric Manifestations: Blockade of reuptake of monoamines

• Strokes: Ischemic and Hemorrhagic

• Vasoconstriction: Adrenergic receptors

• Hemorrhagic: Saccular aneurysms Vascular malformations

• Cell death???
Possible Involvement of free radicals in stimulant-induced toxicity

- DA uptake sites
- \( \uparrow \text{DA} \rightarrow \text{6-OHDA} \)
- \( \uparrow \text{6-OHDA} \rightarrow \text{6-OHDA} \)
- \( \uparrow \text{DA} \rightarrow \text{6-OHDA} \)

RECEPTORS

- KA/AMPA
- NMDA

FREE RADICALS

- \( \uparrow \text{ROS} \)
- \( \uparrow \text{O}_2^- \)
- \( \uparrow \text{H}_2\text{O}_2 \)
- \( \uparrow \text{Glu} \)

METABOLIC PATHWAYS

- Xanthine + \( \text{O}_2 \)
- \( \text{XDH} \)
- \( \text{XO} \)
- \( \text{ONOO}^- \rightarrow \text{ONOOH} \rightarrow \cdot \text{OH} + \text{NO} \)

- \( \text{O}_2^- + \text{H}_2\text{O}_2 \rightarrow \cdot \text{OH} + \text{NO} \)

- \( \text{Glu} \rightarrow \text{NO}^- \)
- \( \text{Glu} + \text{NO}^- \rightarrow \text{ONOO}^- \rightarrow \text{ONOOH} \rightarrow \cdot \text{OH} + \text{NO} \)

- \( \text{Ca}^{++} \)

- \( \text{SOD} \)
- \( \text{Catalase} \)
- \( \text{GSH-Px} \)

- \( \text{H}_2\text{O}_2 \rightarrow \cdot \text{OH} + \cdot \text{OH} \)

- \( \text{Fe}^{++} \)

- \( \text{L-Arginine} \)
- \( \text{NOS} \)

- \( \text{ONOOH} \rightarrow \cdot \text{OH} + \text{NO} \)

- \( \text{ONOO}^- \rightarrow \text{ONOOH} \rightarrow \cdot \text{OH} + \text{NO} \)

- \( \text{ONOO}^- \rightarrow \text{ONOOH} \rightarrow \cdot \text{OH} + \text{NO} \)
Genetic Background

Environmental Background/Life Events

Drug Effects

Toxic/Vascular/Hypoxic

- Neuronal Loss
- Astrocytosis and Microgliosis
- Changes in Cerebral Blood Flow
- Brain White and Gray Matter Structural Alterations

Hypo- and/or hyper-connectivity changes

Cognitive Deficits with Impact on Treatment Responses and Activities of Daily Living
Presentation Outline

• Dopamine systems
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• Cocaine and DA systems
• CUD and neuropsychiatry
• CUD and cognitive findings
• CUD and neuroimaging findings
• Basic mechanisms of CUD complications
• Summary and suggestions
Summary and Suggestions

- Treatment programs need to take into account the cognitive deficits, functional and structural abnormalities that have been associated with chronic cocaine abuse when planning long-term care of these patients.
- Development of cognitive enhancers may be an important approach to treat cocaine use disorder.
- Use of HDAC inhibitors that enhance memory formation may constitute novel approaches to patients who abuse cocaine.
An integrated molecular network model of resilience, addiction, and abstinence

- **Drugs**
  - **Individual Factors** (resilient or susceptible genotypes and phenotypes)
  - **Environment** (resilience or susceptibility factors in family and community members)

- **Changes in Gene Expression**
  - **Epigenetic Alterations**
  - **Differential Changes in Protein Expression**

- **Resilience**
- **Addiction**
- **Abstinence**
Treatment for Cocaine OD or Addiction?
Pharmacogenetics and Vaccines to Treat Cocaine Addiction

Thomas R. Kosten MD
JH Waggoner Chair and Professor of Psychiatry, Pharmacology, Immunology, Pathology and Neuroscience
Baylor College of Medicine and Houston VAMC
Disclosures

• Off label medications without FDA approval for cocaine use disorder will include:
  – Disulfiram, Doxazosin, Anti-cocaine vaccines

• Thomas Kosten MD has consulted with:
  – Alkermes Pharma, Novartis, US World Meds, Braeburn, Indivior, Purdue Pharma
Presentation Outline

• Cocaine pharmacotherapies
  – Disulfiram and Doxazosin (reduce noradrenergics)
  – Noradrenergic pharmacogenetics

• Cocaine vaccines
  – Original cholera vaccine: Partial clinical success
  – New carrier protein: Tetanus
  – New adjuvants: Entolimod
  – Six-fold greater antibody levels
Disulfiram and Doxazosin for Cocaine Pharmacotherapy
Both reduce Norepinephrine

Disulfiram inhibits Dopamine β-hydroxylase (DBH) and reduces Norepinephrine

Pharmacogenetics: Doxazosin & ADRA1A
Adrenergic receptor blocker of acute cocaine effects
Adrenergic receptor blocker (doxazosin) reducing cocaine use
Disulfiram Increases Cocaine-Free Urines (>600 Outpatients in 7 clinical trials)

Disulfiram Decreases Norepinephrine by Inhibiting DBH conversion of Dopamine to Norepinephrine

NE neuron
Inhibit DBH reduces DA to NE conversion
Lower NE for release

NE-responsive Neuron
Alpha-1 receptors

NE = norepinephrine; DA = dopamine.
Doxazosin for Cocaine Use Disorder

• α1-adrenergic blocker of ADRA1A receptor
  – Long-acting, half-life up to 22 hours

• 4 mg doxazosin reduces “high” from 20 and 40 mg IV cocaine in human lab study (n=13)

• 8 mg doxazosin reduces outpatient cocaine use in 2 clinical trials (n=35 and 89)

• Same genetic variant of ADRA1A weakens acute cocaine reinforcement & strengthens outpatient reduction in cocaine use: Pharmacogenetics

Human Lab: Doxazosin Reduces Cocaine “High”

DOX = doxazosin.
Human Lab: Pharmacogenetics
ADRA1A & Doxazosin on Cocaine-Induced “Desire”

Clinical Trials: Doxazosin
Cocaine Abstinence and cocaine (+) Urines

Clinical Trial: Pharmacogenetics
α-1A Adrenergic Receptor & Doxazosin Treatment Response (8 mg daily)

![Graphs showing ADRA1A CC and ADRA1A CT/TT responses to Placebo and Doxazosin over study weeks.]

Personalized Medicine & Doxazosin: Pharmacogenetics of ADR1A1

• Cocaine-free urines increase with doxazosin by 10% and decrease with placebo by 10% for a net **superiority of 20% for doxazosin** in *unselected patients*

• CC genetic variant of ADR1A1 associated with **three-fold more cocaine-free urines** (30% in CC vs 10% in CT/TT variant) with doxazosin

• CC genetic variant of ADR1A1 also associated with **2.5 fold reduced** craving, liking and “high” from cocaine


Anti-cocaine Vaccines

25 years of development
New, much better Vaccines
Antibodies keep drug out of brain
Original cocaine vaccine:
Two Outpatient Randomized, placebo controlled trials

(n=114 and 300)
Cholera toxoid (CTB) carrier
Vaccinated with 5 x 400 µg TA-CD over 12 wks
Blocking antibody level 43 ug/ml binds 80% cocaine
Trial 1: Antibody Response (n=114)
Trial 1: Proportion of Cocaine-free Urines for Weeks 9-17 vs Baseline
Hi vs. Lo antibody vs. Placebo
Trial 2: Antibody (AB) levels & Outcomes (n=300)

- Adequate AB mean of 59 µg/ml at week 16 and 46 µg/ml at week 9; range 10 to 200 µg/ml
- Outcomes & AB levels above 42 µg/ml (vs placebo and low AB level) attained:
  - Better treatment retention: 90% vs 80%
  - More with 2+ wks of abstinence: 3-fold greater
  - % rise cocaine-free urines (vs base wk): 48% vs 8%
- No simple correlation of antibody levels with cocaine-free urines
Developing a new cocaine vaccine

New Carrier: Tetanus vs Cholera toxoid
2-fold increase in AB levels

New Adjuvants: Entolimod vs Alum
3-fold increase in AB levels

Net effect of both improvements
6-fold increase in AB levels
Co-stimulation of TLR-5 & Inflammasome to increase cytokines & antibodies
Cocaine vaccine + Entolimod blocks cocaine-induced locomotion (10 mg/kg)

Total counts (mean ± SEM)

Time (min)

- No vaccine
- TT-SNC + Alum
- TT-SNC + Alum + E6020 + Flagellin
Anti-cocaine Antibody (AB) levels correlate with cocaine induced locomotor activity (cocaine dose 10mg/kg)

\[ R^2 = 0.4834 \]
\[ P = 0.004 \]
Can Someone Smoke Enough to Overcome the Vaccine Titer? Evidence suggests not.
Summary

- **Pharmacogenetic matching** of patients to noradrenergic blockers promises substantially enhanced efficacy of these pharmacotherapies such as Doxazosin.

- **Vaccine with Entolimod** generated SIX-fold more anti-Cocaine antibodies to the NEW cocaine vaccine than to the old, failed cholera-based vaccine.

- **Vaccine with Entolimod** blocked cocaine induced behaviors and preliminary studies have shown excellent human safety of this Entolimod combination vaccine.
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Cleveland Biolabs Inc.
National Institute of Drug Abuse (NIDA)

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