

## **Substance Abuse Division**

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### **Overview**

The Division on Substance Abuse focuses on antecedents and consequences of substance use, abuse, and dependence with particular emphasis on the development and testing of novel approaches to the treatment of substance abuse. A NIDA funded Medication Development Center, now in its 19<sup>th</sup> year, is a major supporter both of treatment research related to opiates, cocaine and marijuana as well as pilot studies for Addiction Psychiatry fellows and young faculty. There are over 30 other funded studies that include clinical trials, human behavioral laboratory studies and imaging and cover all the major illegal drugs of abuse as well as alcohol. Mentoring of fellows and junior faculty to become independent investigators as well as education and training of graduate and medical students and residents is an important part of our mission. The Division has been consistently ranked in the top 3 of Drug and Alcohol programs in the U.S. by U.S. News and World reports issue on medical schools and our Addiction Fellowship program has been funded by NIDA for 20 years.

### **Current Research**

#### **Gillinder Bedi:**

1. Effects of MDMA and THC on social processing: Using fMRI and behavioral tasks to study the acute effects of MDMA and THC on processing of social information in humans.
2. Social Processing in Aging Cocaine Users: Assessing social processing, cognitive function, and brain structural and functional indices in aging cocaine smokers compared to age-matched controls.
3. Neuroeconomics of marijuana use: Using fMRI to examine the neural activity underlying decision-making about marijuana self-administration in marijuana smokers.

#### **Adam Bisaga:**

1. Cocaine Dependence: Examining effects of treatment with levodopa/carbidopa combined with entacapone on reward system function using fMRI and on the abstinence maintenance in cocaine-dependent participants seeking treatment
2. Nicotine Dependence: Examining the effects of pioglitazone in the laboratory model of nicotine dependence and smoking cessation (co-PI with Sandra Comer).

#### **Aimee Campbell, Ph.D.:**

1. Dr. Campbell continues to direct, along with Dr. Edward Nunes, the analysis and manuscript development of the CTN protocol "Web-delivery of Evidence-Based, Psychosocial Treatment for Substance Use Disorders" (CTN-0044; NIDA U10 DA13035 (PI: Nunes). She was PI of a sub-award from the University of North Carolina to conduct secondary analyses of the completed CTN trial "Women & Trauma"; the grant was entitled, "Modeling the Impact

of Group Membership Turnover in Ecologically-Valid Treatment Trials” and was completed in 2012.

**Kenneth Carpenter:**

1. Cocaine Dependence: Developing and testing an experimental paradigm designed to investigate how verbal/cognitive processes promote cocaine use in human laboratory and clinical contexts.
2. Treatment Outcome: Investigating psychological mechanisms predictive of treatment response.

**Stephanie Collins Reed:**

1. Impulsivity in cocaine users: Examining sex differences in the effects of stimulants on a range of impulsivity facets in smoked and intranasal cocaine users compared to healthy controls.
2. Stress response in cocaine users: Examining sex differences in laboratory stress response between smoked and intranasal cocaine users compared to healthy controls.

**Sandra Comer:**

1. Naltrexone for amphetamine and cocaine abuse: Laboratory study examining the utility of naltrexone for treating amphetamine abuse using cocaine as a control drug.
2. Ibudilast for opioid abuse: Laboratory study examining the utility of ibudilast, a phosphodiesterase inhibitor and inhibitor of glial activation, for treating opioid withdrawal symptoms and reducing opioid self-administration.
3. Pioglitazone for opioid abuse and cigarette smoking: Examining the ability of pioglitazone, a medication used to treat Type 2 diabetes, to alter the abuse liabilities of heroin and tobacco (co-PI with Adam Bisaga).
4. Buprenorphine/naloxone for treating pain and opioid abuse: Laboratory study comparing the ability of sublingual buprenorphine/naloxone to treat chronic pain and opioid abuse in different patient populations (opioid abusers with and without chronic pain).
5. Minocycline for treating opioid abuse: Laboratory study supervised by Shanthi Mogali, MD, to examine the utility of minocycline, tetracycline antibiotic and inhibitor of glial activation, in reducing the abuse liability of oxycodone.

**Ziva D Cooper:**

1. Analgesic effects of cannabinoids. Investigating opioidergic contribution to the analgesic and reinforcing effects of smoked marijuana.
2. Cannabinoids and cocaine: Determining the effects of smoked marijuana on smoked cocaine’s subjective and cardiovascular effects.
3. Glial modulators for opioid dependence: Investigating the effects of Ibudilast, a glial cell modulator, on opioid withdrawal, tolerance to opioid-induced analgesia, and self-administration.

**Elias Dakwar**

1. Glutamatergic Modulation of Cocaine-related Deficits: Investigating the effect of glutamatergic modulation on choice behavior and relapse risk in cocaine dependent individuals.

**Richard W. Foltin:**

1. Hypocretin (Orexin): Investigating the effects of hypocretin agonists and antagonists on drug taking and feeding behavior with the goal of understanding potential therapeutic uses of hypocretin agents.

2. Using expected utility theory to measure motivational effects of cocaine abstinence: Developing novel procedures for studying relapse.

**Margaret Haney:**

1. Marijuana Dependence: Testing the effects of medications (zolpidem and varenicline, administered alone and in combination with nabilone) on marijuana self-administration, withdrawal and relapse.
2. Cocaine Dependence: Testing the effects of modafinil on cocaine relapse as a function of DRD4 polymorphism and the presence of cocaine-paired cues and a noncontingent cocaine administration.

**Jermaine Jones**

1. Effectiveness of naloxone distribution programs in New York City. Collected data on the ability of standard NYS DOH overdose response training to improve accurate identification of opioid overdose and proper administration of naloxone among active heroin users.
2. Contribution of Various Genetic Polymorphisms to the Abuse Liability of Oxycodone: This K01 study attempts to identify genetic variants responsible for divergent physiological and subjective responses to opioids.

**Herbert D. Kleber**

1. 19<sup>th</sup> year of his NIDA funded P-50 Medication Development Center Grant. Has 2 cores and 5 projects, which are, described elsewhere
2. Working with Elias Dakwar to carry out a pilot project on a new approach for withdrawal from buprenorphine maintenance

**Frances R. Levin**

1. Treatment of Cocaine Dependence: Multi-site trial comparing the cocaine vaccine to a placebo vaccine.
2. Combined Pharmacotherapies for Cannabis Dependence: The combined pharmacotherapy of the cannabinoid receptor agonist dronabinol and the alpha-2 agonist lofexidine in conjunction with weekly Motivational Enhancement (MET) and Relapse Prevention (RPT) therapy.
3. Attention-Deficit/Hyperactivity Disorder (ADHD) and Cocaine Dependence: Lead site of a multi-site trial examining 2 doses of mixed amphetamine salts-extended release compared to placebo for the treatment of cocaine-dependent adults with ADHD.
4. Research Fellowship in Substance Abuse Disorders: Provides research and academic psychiatrists with the skills and clinical experience necessary to advance our knowledge about the etiology and treatment of substance abuse disorders.

**John Mariani:**

1. Alcohol Dependence Treatment: Testing gabapentin for abstinence initiation in alcohol dependence.
2. Treatment of Cannabis Dependence: Testing quetiapine for treatment of cannabis dependence.

**Diana Martinez:**

1. Kappa opioid receptor in cocaine dependence: Using PET to investigate kappa receptor binding and its correlation with negative reinforcement in cocaine dependence.
2. Metabotropic glutamate receptor 5 in cocaine dependence: The MgluR5 receptor is being imaged with PET in cocaine abusers and matched controls.

3. Imaging dopamine transmission and kappa receptors in binge alcohol drinkers: Investigating alterations in kappa receptors in young adult binge drinkers.
4. Repetitive transcranial magnetic stimulation (rTMS) in cocaine dependence: Investigating the effect of rTMS on cocaine seeking behavior in cocaine-dependent participants.

**Edward Nunes**

1. Drug Abuse Treatment Development and Research Mentoring Career Development Grant (K24): a competing renewal application was funded in 2012 (NIDA K24 DA022412); funding allows Dr. Nunes to continue to expand his program of research and research mentorship in the field of drug abuse treatment development.
2. Clinical Trials Network (CTN) Grant: NIDA Clinical Trials Network (CTN) Greater New York Node cooperative agreement (NIDA U10 DA13035) is in its 12<sup>th</sup> year under the multiple PI mechanism (NYU CTN program; Co-PI: John Rotrosen, MD). With 12 collaborating community treatment programs, the Node has completed 20 clinical trials (4 of which the Greater New York Node was a national leader in) and has over 120 publications and 300+ presentations. Most recently, a trial of a web-based intervention (Therapeutic Education System (TES)) was completed at 10 sites nationally, as well as the "Cocaine Use Reduction with Buprenorphine (CURB)" protocol that was conducted at the Albert Einstein College of Medicine, Division on Substance Abuse. There are 3 new multi-site trials that are in the planning stage, one of which the Greater New York Node is leading. See <http://www.ctndisseminationslibrary.com> or visit Facebook (<https://www.facebook.com/?ref=home#!/ctnlibrary>) for more information.
3. Training Clinicians in Motivational Interviewing Grant: Dr. Nunes and his team have completed the pilot phase for the "Training Clinicians in Motivational Interviewing" grant (NIDA R01 DA 016950; PI: Nunes); the main trial is underway.
4. Injectable Depot Naltrexone for Treatment of Opioid-Dependent Parolees and Probationers Grant: Participants continue to be recruited for a collaborative R01 (NIDA R01 DA24554, PI: Nunes) protocol, "Injectable Depot Naltrexone for Treatment of Opioid-Dependent Parolees and Probationers: A Controlled Effectiveness Trial" at the STARS program. Charles O'Brien, MD, PhD at the University of Pennsylvania is coordinating the national trial.

**Wilfred Raby:**

1. Depressed cocaine-dependent patients: Investigation of stress parameters and treatment outcomes in a clinical trial of mirtazapine
- 2: Cocaine Dependence: Investigation of mifepristone on stress sensitivity and relapse-risk in cocaine dependent men.

**Jennifer Smith, Ph.D.:**

Dr. Smith is the Project Director for a grant to develop improved methods for training community-based clinicians in Motivational Interviewing based on the technique of live supervision (NIDA R01 DA016950; PI: Nunes).

**Maria Sullivan**

1. Opioid abuse in chronic pain patients: Translational research combining human behavioral laboratory testing of oxycodone effects in Buprenorphine/Naloxone (suboxone) maintained patients and a clinical trial using this (suboxone) as novel treatment for co-occurring opioid addiction and chronic pain.

2. New antagonist therapy for opioid dependence: Testing long-acting injectable naltrexone (Vivitrol) in monthly injections vs. oral naltrexone maintenance in a trial incorporating behavioral treatment.

#### **Nehal Vadhan:**

1. Marijuana use and psychosis. Comparing marijuana's acute subjective and neurocognitive effects in marijuana smokers who are at-risk for a psychotic disorder (i.e., prodromal) and those who are not.
2. Stimulus-response learning in cocaine users. Examining reward- and nonreward-based stimulus-response learning in cocaine abusers and controls.

#### **Stanislav R. Vorel**

1. Glutamatergic Modulation of Exposure Therapy in Cigarette Smoking: Examines the effects of pharmacologically enhanced smoking cue exposure therapy as augmentation strategy for nicotine replacement in the treatment of nicotine dependence.
2. NMDA Glutamate Receptor Transmission in Extinction of Cocaine-Seeking Behavior: Examines the effects of pharmacological manipulations of NMDA receptor neurotransmission on cocaine cue extinction training in rats.
3. Pharmacological enhancement of contingency management training in the male rat: Examines the effects of pharmacological manipulations of dopamine neurotransmission in a rat model of contingency management training

### **Education and Training**

Dr. Levin's T32 "Research Fellowship in Substance Abuse Disorders" will begin its 21<sup>st</sup> year this July 1<sup>st</sup>. It received a "1" in grant review, the highest score possible.

### **Honors and Awards**

**Gillinder Bedi** received a K23 in 2013 titled "Neurobehavioral mechanisms of decisions to smoke marijuana and cocaine in humans".

In 2012, a paper by Dr. Bedi was shortlisted for the Society of Biological Psychiatry 2012 Ziskind-Somerfeld Research Award.

In 2012, Dr. Bedi received a NYSPI Research Associate's Award.

**Aimee Campbell** became a member of the College on Problems of Drug Dependence in 2012.

**Stephanie Collins Reed** was named Chair of the CPDD Travel Awards and Mentoring Committee

**Sandra Comer** is Co-I and has a sub-contract on an R01 grant awarded to Traci Green at Brown University entitled "Extending Naloxone Access Through Strategic Alliances for Medications Development."

**Ziva D Cooper** This past year, I was accepted into the International Cannabinoid Research Society and the American Society (ICRS) for Pharmacology and Experimental Therapeutics (ASPET). With Margaret Haney, we successfully applied for and received funds for a symposium for the 2013 ASPET meeting, which met jointly with the British Pharmacology Society. Our symposium was titled "The Opioid-Cannabinoid Connection: A Translational, Behavioral Perspective," and included both American and international experts in the field including Drs. Aron Lichtman (Virginia Commonwealth University), David Finn (National

University of Ireland), Zuzanna Justinova (NIDA, IRP, NIH), and our own Adam Bisaga (Columbia University). I was also a speaker at the symposium and discussed our human laboratory studies investigating opioid-cannabinoid interactions.

**Suzette Evans** is the Editor of Experimental and Clinical Psychopharmacology and on the Board of Convention Affairs of the American Psychological Association.

**Richard W. Foltin** Received Department of Psychiatry Marian W. Fischman Award

**Margaret Haney** was elected to the Board of Directors for the College on Problems of Drug Dependence and became a Member of the American College of Neuropsychopharmacology.

**Jermaine Jones** NIDA Minority Work Group: CPDD Travel Award, 2012.

American College of Neuropsychopharmacology: Early Career Travel Award, 2012

**Herbert D. Kleber** presented two Grand Rounds, serves on the APA Council on Addiction, the Betty Ford Institute Executive Council, University of Michigan Monitoring the Future Scientific Advisory Board, OASAS Medical Advisory Board, Invited lecture at Dartmouth, among others. Listed in best Doctors in America and Best Doctors in the Metro New York area. Invited commentary in Am. J. of Psychiatry “Physicians and Medical M.J.”

**Frances Rudnick Levin** was 2012 Best doctors- New York Magazine

President- American Academy of Addiction Psychiatry

Working with AAAP’s Executive Director, Dr. Levin obtained a 5 year NIDA conference grant for AAAP’s annual meeting

**John Mariani**: Obtained an R21 from the NIAA entitled Testing Gabapentin for Abstinence Initiation in Alcohol Dependence.

**Edward Nunes** received a competing continuation for the NIDA Clinical Trials Network (CTN) Grant, and was appointed Co-Chair of the Institutional Review Board of the New York State Psychiatric Institute-Columbia University Department of Psychiatry.

**Wilfrid Noel Raby** was chosen as a “Best Doctor in New Jersey” and “America’s Top Psychiatrists” in 2012.

**Maria Sullivan and Adam Bisaga** received a 5-year RO1 from NIDA entitled "Improved Strategies for Outpatient Opioid Detoxification.

**Nehal Vadhan** was a finalist for the “Top Poster” Award at the 2012 meeting of the Society of Biological Psychiatry (“Probabilistic category learning is associated with dopamine D2 receptor availability in the ventral striatum of cocaine users)

## Publications (Selected)

1. Foltin, R.W. The Behavioral Pharmacology of Anorexigenic Drugs in Non-human Primates: 30 Years of Progress. Behavioural Pharmacology 23:461-477, 2012.
2. Kleber, H.D., & DuPont, R.L.: Physicians and Medical Marijuana. American Journal of Psychiatry. 169: 564-568, 2012.
3. Levin FR, Mariani J, Brooks DJ, Pavlicova M, Nunes EV, Agosti V, Bisaga A, Sullivan MA, Carpenter KM. (2013). A randomized double-blind, placebo controlled trial venlafaxine extended release for co-occurring cannabis dependence and depressive disorders. Addiction. Jan 8. doi: 10.1111/add.12108. [Epub ahead of print] NIHMSID: 434164 (PMCID in progress)

4. Reed, S.C., Levin, F.R., Evans, S.M. Alcohol increases impulsivity and abuse liability in heavy drinking women. *Exp. Clin. Psychopharmacol.* 2012, 20, 454-465. PMID: 448051. PMCID in progress.  
Cooper, Z.D., Foltin, R.W., Evans, S.M. Effects of menstrual cycle phases on cocaine self-administration in rhesus macaques. *Hormones & Behavior.* 63: 105-113. PMCID in progress, 2013.
5. Smith JL, Carpenter KM, Amrhein PC, Brooks AC, Levin D, Schreiber EA, Travaglini LA, Hu MC, Nunes EV. Training substance abuse clinicians in motivational interviewing using live supervision via teleconferencing. *J Consult Clin Psychol*, 80(3), 450-64, 2012.

## **Divisional Highlights**

### **Adam Bisaga**

1. Levodopa/carbidopa/entacapone can be safely administered in combination with smoked cocaine

Adding memantine does not appear to increase the effectiveness of injectable XR naltrexone in treatment of participants with opioid dependence and may lead to an increase in treatment drop-out.

### **Gillinder Bedi**

1. Distributed patterns of neural activation predict choices to self-administered marijuana in humans with a high degree of accuracy.
2. Computer-based categorization of the meaning and structure of free speech can be used to measure alterations to mental state arising from intoxication with MDMA (ecstasy) and methamphetamine.

### **Kenneth Carpenter**

1. Experiential Avoidance is associated with the amount of cannabis use among treatment seeking cannabis dependent patients and predicts poor clinical prognosis among opiate dependent patients receiving outpatient treatment.

### **Stephanie Collins Reed:**

1. Laboratory measures show that cocaine users are more impulsive than controls; smoked cocaine users had higher measures of impulsivity than intranasal cocaine users.  
Stress response is greater in controls than smoked cocaine users and in females compared to males
2. Laboratory stress increases heart rate and cocaine craving in cocaine users compared to a stress-free condition but does not increase cocaine self-administration

### **Sandra Comer:**

1. Naltrexone did not alter the positive subjective effects of smoked cocaine, but it did reduce craving for cocaine.
2. Minocycline reduced the positive subjective effects of oxycodone.

### **Ziva D Cooper:**

1. Acute naltrexone administration increases the positive subjective effects of marijuana
2. Both dronabinol and smoked marijuana decrease the response to a acute painful stimulus.

3. Ibudilast decreases some symptoms of opioid withdrawal in opioid-dependent volunteers

**Suzette Evans:**

1. Alcohol increases impulsivity and abuse liability in moderate drinking women.
2. An adenovirus-based anti-cocaine vaccine effectively blocked cocaine reinstatement in a pre-clinical model. Sex differences were observed in stress-induced increases in heart rate, with women in the luteal phase (when progesterone is elevated) showing the most protective response

**Richard W. Foltin:**

1. Consumption of large meals of highly palatable food decreases the anorectic effects of drugs that increase serotonin. Because serotonin release is associated with naturally occurring satiation these findings suggest that eating large meals decreases the rate of satiation leading to further increases in meal size and obesity.

**Margaret Haney:**

1. Nabilone administration robustly decreased both marijuana withdrawal symptoms and a laboratory measure of marijuana relapse.
2. Daily marijuana smokers who also smoke cigarettes have high rates of marijuana relapse, and cigarette smoking versus recent abstinence does not directly influence this association. These data indicate that current cigarette smoking is a clinically important marker for increased risk of marijuana relapse.

**Jermaine Jones:**

1. Brief overdose prevention training significantly improved the ability of heroin users to accurately identify signs of opioid overdose and scenarios where naloxone administration was indicated.

**Frances Rudnick Levin**

1. Dr. Levin carried out the first pharmacologic clinical trial targeting adults with cannabis dependence and depression. Compared to placebo, venlafaxine was not superior to placebo in reducing depressive symptoms. Notably, higher doses of venlafaxine were associated with lower marijuana abstinence rates than placebo.

**John Mariani:**

1. The combination of mixed amphetamine salts-extended release and topiramate is more effective than placebo in achieving abstinence among cocaine-dependent adults who are more frequent users of cocaine.

**Diana Martinez:**

1. Dopamine transmission in the striatum was blunted in cocaine-dependent subjects who failed to respond to treatment. Participants who responded successfully to treatment had higher dopamine transmission, similar to that seen in controls.
2. Heroin-dependence is associated with deficits in dopamine transmission, similar to that seen in other types of addiction.

**Wilfred Raby**

Dysregulation of stress physiology as measured by alterations in diurnal cortisol secretion profile was associated with inability to attain abstinence during a lead-in period to a

clinical trial for depressed cocaine abusers, despite high value voucher incentives contingent on abstinence (Am. J. Addiction, in press).

**Jennifer Smith**

Dr. Smith received a faculty appointment as an Assistant Professor of Clinical Psychology, Columbia University College of Physicians and Surgeons

**Maria Sullivan:**

1. In Buprenorphine/Naloxone (Suboxone) maintained chronic pain patients with a history of opioid abuse, oxycodone enhanced analgesic effects of this (Suboxone) but failed to serve as a reinforcer, suggesting that can safely be combined with shorter-acting opioids for pain management in patients with a history of opioid abuse.
2. A single injection of a long-acting naltrexone at completion of detoxification, results in 50% 6-month retention on oral naltrexone, effectiveness comparable to Suboxone maintenance treatment.

**Nehal Vadhan:**

1. Marijuana users at clinical high-risk for a psychotic disorder show prolonged intoxication and increased psychotic-like and rewarding effects following smoked marijuana, relative to marijuana smokers who are not a risk, under controlled laboratory conditions.