

## Medications Development Centers (MDC)

The following are the Medications Development Centers currently part of the NNP. These abstracts are derived from the NIH CRISP query system. More information is available through CRISP at <http://crisp.cit.nih.gov/> and through the Principal Investigator.

### Cocaine Pharmacotherapy Targeting Dopamine & GABA

Baylor College of Medicine  
 Dept. of Psychiatry & Behavioral Sciences  
 1 Baylor Plaza  
 Houston, TX 77030-3498  
 Thomas R. Kosten, M.D.  
[kosten@bcm.edu](mailto:kosten@bcm.edu)

This Center for Medications Development (MDU) has a theme of developing new GABA enhancing medications and using genetic approaches to optimally match successful cocaine pharmacotherapies such as disulfiram and the GABA reuptake blocker tiagabine to subgroups of cocaine dependent patients. We are conducting two outpatient randomized clinical trials and a series of five laboratory screening studies for new GABA enhancers. The first project is a randomized, placebo-controlled, 12-week clinical trial examining 150 cocaine-dependent methadone-stabilized patients in a trial of disulfiram and the GABA reuptake blocker tiagabine. The second project includes 140 depressed, recently abstinent, cocaine-dependent patients in a randomized, placebo-controlled, 12-week relapse trial with four treatment groups: placebo, sertraline, sertraline + tiagabine and sertraline + gabapentin. The patients in both projects will undergo genetic screening of GABA related polymorphisms as potential predictors of treatment response to GABA enhancers in future studies. The third project will use cocaine administration to humans in a laboratory in order to screen five GABA enhancers for their potential utility as pharmacotherapies. Overall, over 300 patients will be studied in this Center and eight different agents in either outpatient Phase II trials or human laboratory studies. Keywords: Clinical trial, cocaine, dopamine, drug abuse chemotherapy, drug addiction, gamma aminobutyrate, human therapy evaluation clinical research, human subject, patient oriented research

### Center for Research Improving Treatment of Drug Abuse

University of Pennsylvania School of Medicine  
 Dept. of Psychiatry  
 Treatment Research Center  
 3900 Chestnut Street  
 Philadelphia, PA 19104  
 Charles P. O'Brien, M.D.  
[obrien@mail.trc.upenn.edu](mailto:obrien@mail.trc.upenn.edu)

This is a P60 Center that was formed in 1987 with the theme of improving treatment of addiction. A major focus of this Center is its multiple educational programs for medical students, residents, undergraduates, postdoctoral fellows, minorities, community clinicians, probation officers, judges and legislators. As expected of a P60, we have always had a basic research component with an eye toward translation of findings from the lab to the clinic through clinical trials and the translation of technology from clinical trials to the community practitioner. Our ultimate goal is to have an impact on clinical practice in the management of addictive disorders. Thus the over-arching theme of this Center has always been research that results in improvement of treatment of substance abuse. Project 1 is a basic project addressing opiate addiction by a study of Mu Opiate Receptor Interacting Proteins using well characterized samples obtained from patients in our clinical trials and NIH sources. Project 2 addresses the growing problem of prescription opioid abuse by conducting a longitudinal study of primary care patients beginning treatment with opioids for chronic pain. Projects 3 and 4 address cocaine addiction and the spread of HIV. Project 3 proposes the study of an adaptive treatment for cocaine dependence; and Project 4 is a clinical trial of modafinil in women involved in trading sex for cocaine. Two proposed pilot projects focus on brain imaging of craving in marijuana and nicotine dependent patients using strategies developed in our prior studies of cocaine and opiate addiction. Keywords: Drug abuse chemotherapy, drug abuse therapy, marijuana, nicotine, dependence, cocaine, HIV, opiate receptor, primary care, clinical trial, patient oriented research

### Innovative Approaches for Cocaine Pharmacotherapy

University of Pennsylvania School of Medicine

Dept. of Psychiatry  
Treatment Research Center  
3900 Chestnut Street  
Philadelphia, PA 19104  
Helen M. Pettinati, Ph.D.  
pettinati\_h@mail.trc.upenn.edu

This is a NIDA-funded P50 Research Center that serves as one of NIDA's Medication Development Units (MDU). The theme of our MDU is testing innovative medication combinations for managing "hard-to-treat" cocaine/alcohol dependent patients. Previously our P50 focused primarily on several types of severe cocaine dependence, but patients with the combined dependence have become most common. This group responds poorly to existing treatments and has received little research attention in the past. The MDU CORE coordinates the components, conducts an active pilot program, provides a structure for mentoring young, career investigators who want to specialize in cocaine research, and has priority access to important on-site resources: (1) General Clinical Research Center (GCRC) - an inpatient facility for conducting safety trials; (2) Center bio-statistician; (3) web-based Data Management Unit, and (4) a specialty drug screen lab. The proposed components in this application reflect developing prototypes, which contain descriptions of specific projects to be done over the next 5 years. Basically, projects are arranged to allow for novel medications to be systematically studied in human subjects (normal controls and patients) from safety through efficacy. Component 1 evaluates a promising novel compound, topiramate, in a randomized, placebo-controlled trial. Component 2 describes a series of safety/tolerability monitoring studies that are necessary prior to combining medications in a large clinical trial. Component 3 operationalizes a large controlled trial to evaluate the efficacy of combination medications in cocaine-alcohol dependent patients. Component 4 describes a model that identifies potential individual genetic predictors to medication response. Keywords: Cocaine, drug addiction, drug addiction antagonist, drug screening/evaluation, human therapy evaluation, clinical research, human subject

#### Methamphetamine Pharmacotherapy Development Center

California Pacific Medical Center Research Institute  
Addiction Pharmacology Research Laboratory  
St. Luke's Hospital, 7th Floor  
3555 Cesar Chavez Street  
San Francisco, CA 94110  
John Mendelson, M.D.  
mendelje@cpmcri.org

Methamphetamine abuse is a widespread problem for which there is currently no effective pharmacotherapy. This project will test the safety and efficacy of medications that modulate adrenergic function as treatments for methamphetamine dependence. In a coordinated series of inpatient laboratory and outpatient treatment studies, we will perform a systematic investigation of the utility of adrenergic compounds. The specific compounds that we propose examining are the alpha-2 agonist clonidine, the beta-blocker carvedilol, the alpha-1 antagonist prazosin, and the norepinephrine reuptake inhibitor atomoxetine. As part of our research, we will develop new assay techniques and utilize population pharmacokinetic/pharmacodynamic modeling to provide a quantitative estimate of the amounts of illicit methamphetamine consumed during our trials. We postulate that quantifying the effects of candidate pharmacotherapies on illicit drug intake will substantially improve our ability to assess the effectiveness of our medications and therapeutic outcomes. Specific experiments are coordinated so that results from one experiment informs the design of subsequent studies. In our laboratory component we will (1) assess interactions between our candidate drugs and methamphetamine, (2) develop and validate under controlled conditions our method to quantify illicit drug intake, and (3) evaluate methamphetamine-cytokine interactions. Results from these studies are used to advance two of the four adrenergic drugs from the inpatient laboratory to placebo-controlled outpatient treatment trials. In these outpatient trials we will (1) assess the clinical efficacy of these candidate drugs, (2) validate the quantitative methamphetamine ingestion method under real world conditions, and (3) determine the utility of our immune markers to predict relapse. Keywords: Adrenergic agent, drug abuse chemotherapy, drug addiction, drug screening/evaluation, methamphetamine clinical research, human subject, patient oriented research

#### Novel Medications Approaches for Substance Abuse

New York State Psychiatric Institute  
1051 Riverside Drive  
New York, NY 10032

Herbert D. Kleber, M.D.  
hdk3@columbia.edu

The current MDRC has as its major themes the development of effective medications for subgroups of the addict population, the search for better methods to identify them, and the development and evaluation of medications for emerging problems. The renewal consists of two Cores and five Projects, among which there is considerable interaction. Project 1 uses the heroin self-administration model developed in the initial MDRC to evaluate prescription opioids, alone and in combination with buprenorphine. Project 2 combines innovative imaging of the D1 and kappa opioid receptors (KOR) with our model of cocaine self-administration to investigate whether the D1 and KOR receptor availabilities will be predictive of vulnerability to cocaine-induced cocaine-seeking. Project 3, using the targeted subgroup model and innovative design features, will use an abstinence-induction method to further assess the efficacy of venlafaxine in cocaine abusers with primary depression. Project 4 (based on laboratory data from Project 5 and a Center-funded pilot study) proposes a clinical trial to determine if dronabinol will reduce marijuana withdrawal symptoms and improve marijuana abstinence in marijuana-dependent individuals. Project 5 proposes to develop a model of marijuana relapse in order to study the effects of potential treatment medications (oral THC, nefazodone, the cannabinoid receptor antagonist SR 141716) with marijuana abusers, evaluating agents that may either ameliorate marijuana abstinence symptoms or reduce marijuana's acute effects. Overall, the Center has the potential to develop better medications and models for treating abuse of these three drugs, and, to meet this goal, has the unique ability to rapidly move back and forth between human laboratory and clinical studies. Keywords: Cocaine, combination chemotherapy, drug abuse chemotherapy, heroin, marijuana abuse clinical research, human subject

Substance Abuse Research & Medications Development Center

University of Texas Health Sciences Center  
Box 20036  
Houston, TX 77225  
F. Gerard Moeller, M.D.  
frederick.g.moeller@uth.tmc.edu

Cocaine abuse alone, and co-occurring with heroin dependence, have substantial individual and societal consequences. The Substance Abuse Research Center group, Department of Psychiatry, University of Texas Health Science Center-Houston and the Center for Addiction Research, University of Texas Medical Branch-Galveston, are devoted to development and screening of effective pharmacotherapies. Activities include Scientific/Administrative oversight, and implementation of specific preclinical, human laboratory, CRC inpatient, and Treatment Research Clinic outpatient studies. The themes include medication screening and development, specification of intervention points in disease course (ongoing v abstinence), and delineation of optimal medications alone and in combination. The research and clinical activity include a substantial interdisciplinary training component. The aims will be accomplished through four component projects listed below: (1) Scientific Project-Cocaine/Heroin: Pharmacotherapy Dosing Regimens, (2) Scientific Project-Screening Medications for Cocaine Cessation and Relapse Prevention, (3) Scientific Project-Impulsivity, Brain Function & Substance Abuse Treatment, and (4) Scientific Project-Drug Effects on Oral cocaine-Reinforced Behavior. Keywords: Cocaine, drug abuse chemotherapy, drug addiction, substance abuse related disorder, therapy design /development clinical research

UCLA Medication Development Unit for Stimulant Abuse

University of California, Los Angeles  
David Geffen School of Medicine  
Dept. of Family Medicine  
10880 Wilshire Boulevard,  
Suite 1800  
Los Angeles, CA 90095-9087  
Steven Shoptaw, Ph.D.  
shoptaw@mednet.ucla.edu

The thematic emphasis that unifies this continuation of the existing Medication Development Unit for Stimulant Abuse is the development of pharmacological treatments for stimulant abuse through comprehensive and efficient methodologies. The activities will involve an ever greater linkage of Phase I with Phase II work, a stronger effort to apply advanced biostatistical methods to isolate effects of missing data and to identify potential medication effects in subgroups, more effort to develop biomarkers that discriminate meaningful differences in outcomes, and more focus on the evaluation of

medications within the context of carefully specified and timed behavioral interventions. This P50 Center continuation proposes Phase I and Phase II research projects that will complete the development of four medications for methamphetamine abuse from initial stages of safety/interaction through preliminary efficacy trials. The Specific Aims are: (1) to identify and test novel medications for the treatment of stimulant abuse and dependence; (2) to conduct Phase I and Phase II trials of approved medications and novel compounds with potential for the treatment of stimulant-related disorders, in the context of concurrent behavioral treatments; and (3) to improve the efficiency of conducting medications research by using best practices and by applying cutting-edge biostatistical methods when analyzing trials data, creating a resource available to the field as a center of excellence in the area of clinical trials for stimulant abuse and dependence. Keywords: Central nervous system stimulant, drug abuse, drug abuse chemotherapy, drug screening /evaluation, human therapy evaluation, methamphetamine clinical research, human subject, patient oriented research