Poster #11

Help-Seeking Behaviors of African American Mothers Who Use Cocaine: A Qualitative Analysis

Ann M. Cheney, G.M. Curran, B.M. Booth, T. Borders

This poster presents research on the barriers and facilitators to seeking substance use treatment services among African American mothers using cocaine. We conducted semi-structured interviews with 24 African American women to explore perceived need for substance use treatment. Using grounded theory techniques, a team of qualitative experts identified key themes regarding the common barriers and facilitators to accessing substance use treatment programs among cocaine using mothers. Based on the women's narratives, we found that fear of losing children, desire to be a good mother, strong support systems, and positive encouragement from recovered women encouraged them to consider treatment and facilitated, for some, entry into treatment. Resistance to leaving children, limited financial and social resources, and doubt in treatment efficacy created barriers for those seeking treatment. The findings indicate that interventions need to consider the unique role that motherhood plays, as a facilitator and barrier, in women's help-seeking behaviors.

UAMS

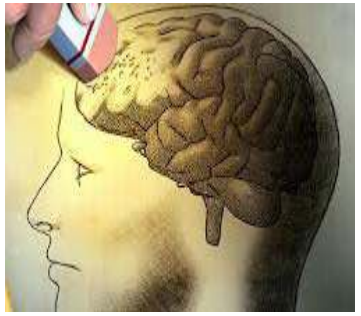
COLLEGE OF MEDICINE

UNIVERSITY OF ARKANSAS FOR MEDICAL SCIENCES

UAMS College of Medicine Series

Showcase of Medical Discoveries:

A Focus on Substance Abuse



Thursday,
December 5, 2013
4:00—5:30 p.m.

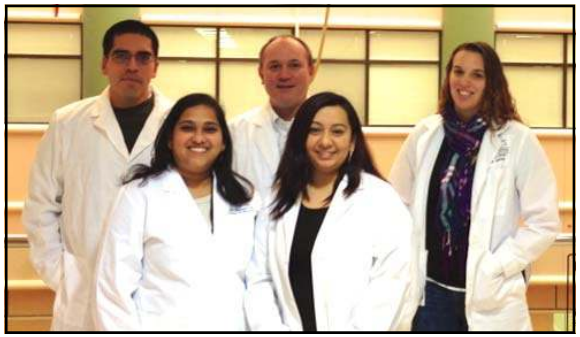
Winthrop P. Rockefeller
Cancer Institute
Rotunda (10th Floor)

A wine and cheese reception featuring UAMS investigators discussing their research and discoveries.

Poster #1

Developing Novel Nanotherapies for the Treatment of Methamphetamine Addiction

Nisha Nanaware-Kharade, Emily E. Reichard, Shradda Thakkar, Guillermo A Gonzalez III, Reha Celikel, Kottayil I. Varughese, Eric C. Peterson



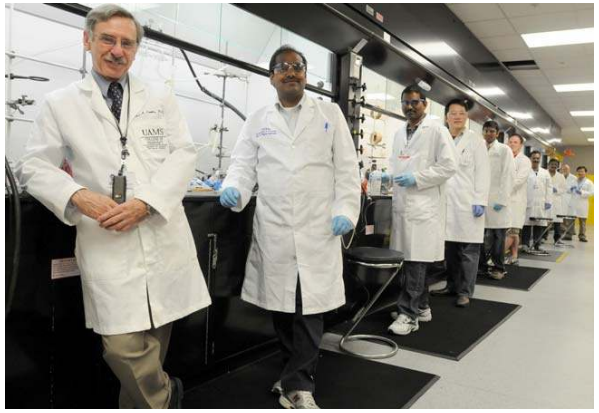
Background: Methamphetamine (METH) abuse is a serious problem in the US and worldwide, with associated devastating socioeconomic consequences for individuals, families, and communities. There are no FDA-approved medications available for treatment. Methamphetamine acts on multiple sites in the brain, and efforts to design drugs that protect against the effects of METH have not been successful. Thus, current METH abuse treatment is mainly limited to supportive behavioral therapy with no pharmacological aid to help patients avoid relapse to drug use. Unfortunately, most patient do relapse to METH use at some point. Thus, discovery of new treatments that could help patients avoid relapse, or blunt the rewarding effects from reinitiating drug use is of primary importance.

Results. We are combining antibody therapy and nanotechnology to generate an adaptable range of anti-METH medications that will have applicability to important therapeutic treatment (e.g., a short-acting medication for overdose and a long-acting low volume of distribution medication needed for chronic treatment of addiction). We are accomplishing this through the use of nanotechnology and advanced protein modification with inert polymers. These studies will provide the first detailed information on the necessary design features and molecular principles required to create advanced new generations of novel nano-therapeutics for the treatment of drug abuse. In a second collaborative project with researchers in the UAMS Department of Physiology and Biophysics, we are using x-ray crystallography to determine the molecular structure of our highest activity anti-METH antibodies. We are using the resulting structural data and recombinant molecular technologies to engineer a new generation of antibodies with enhanced efficacy against METH.

Poster #10

Development of New Oral Medications for the Treatment of Methamphetamine Addiction.

Peter A Crooks, Guangrong Zheng, Linda P. Dwoskin, Michael T. Bardo, David B. Horton, Justin R. Nickell, Andrew C. Meyer, Nichole M. Neugebauer, Agripina G. Deaciuc, Carrie E. Wilmouth, Kristin M. Alvers, Joshua S. Beckmann, Emily D. Denehy, Kiran B. Siripurapu.



Methamphetamine abuse continues to escalate in the US, and there are currently no therapeutic products available for the treatment of methamphetamine addiction. The overall objective of our drug discovery research is to identify orally active small molecule clinical candidates for the treatment of methamphetamine abuse. Recently, we have discovered a novel chemical entity (GZ-793A), which potently and selectively interacts with and inhibits the function of a new target protein, the vesicular monoamine transporter-2 (VMAT2), located in the central nervous system. This transporter is an important player in the mechanism of methamphetamine's action as a stimulant, and promotes dopamine (a neurotransmitter responsible for the rewarding and addictive effects of methamphetamine) release from nerve terminals in the brain after exposure to methamphetamine. Our hypothesis is that potent and selective inhibitors of VMAT2 function can provide the requisite preclinical behavioral profile for clinical evaluation as a pharmacotherapy for methamphetamine abuse. We have shown that GZ-793A exhibits potency and selectivity in decreasing methamphetamine-evoked dopamine release from nerve terminals, and decreases the rewarding effects of methamphetamine in a methamphetamine-addicted animal model. Our goal is to develop GZ-793A as a high value clinical candidate and the first small molecule therapy for the treatment of methamphetamine addiction.

Poster #9

Implementation of a Tobacco Cessation Program in a Multidisciplinary Oncology Clinic

Matthew A. Steliga, Claudia P. Barone, Erna L. Boone, Patricia L. Franklin, Virginia E. Hullihan

Many patients in a thoracic surgery oncology clinic smoke. Unaided cessation has a poor success rate (<5%), while physician recommendation, counseling by certified tobacco treatment specialists (TTS), pharmacotherapy and follow up may improve quit rates.

Any patient actively smoking underwent brief intervention by the surgeon and was referred to a TTS. The counseling took place in a private room in clinic. Exhaled carbon monoxide monitoring confirmed use and cessation. Pharmacotherapy was selectively used.

Sixty smokers underwent intervention by the surgeon and referral to the quitline and in-clinic TTS. Despite physician recommendation, the free service, and convenience in clinic, only 24/60 agreed to meet with the TTS, enroll in the program, and agreed to follow up. For those who did, 17/24(70.8%) quit and remained abstinent (1-6 month follow up).

Integrating TTS in a multidisciplinary surgery oncology clinic can be accomplished. For those that enroll and consent to follow up, pilot data demonstrate excellent short-term quit rates in this setting. Ongoing enrollment, further follow up, and planned expansion to involve other clinics will allow better understanding of the efficacy of tobacco cessation services integrated into clinical settings.

Poster #2

Cocaine Dependence and Childhood Maltreatment are Associated with Altered Configurations of Personality Traits

Lisa K Brents, Shanti Prakash Tripathi, Jonathan Young, G Andrew James, Clinton D Kilts , Helen L. Porter, James T. Dyke

Background: Addictions are debilitating disorders that are highly associated with personality abnormalities. Early life stress (ELS) is an established risk factor for addiction and personality disturbances, but the behavioral and neural representations of the relationships between addiction, ELS and personality organization are poorly understood.

Methods: Ninety-five research participants (37 females, mean age 37.8 ± 8.8) were assessed for cocaine dependence (-/+) and ELS history (-/+) and were grouped factorially. NEO-FFI personality measures were compared between the groups to examine addiction- and ELS-related personality differences. The k-means clustering method was used to uncover personality configurations within the sample; these clusters were stratified across subject groups.

Results: Trait expression differed significantly across subject groups. Cocaine-dependent subjects with a history of ELS (cocaine+/ELS+) displayed significantly greater neuroticism and lower openness, agreeableness, and conscientiousness than controls (cocaine-/ELS-). The cluster analysis resulted in four distinct personality profiles: Open, Gregarious, Dysphoric, and Closed. Distribution of these profiles across subject groups differed significantly. Most cocaine-dependent subjects were either Dysphoric or Closed; the cocaine-/ELS+ group was predominately Open, and the cocaine-/ELS- (control) group was predominately Gregarious. Future work will explore the neural representations of these personality groups using resting-state functional magnetic resonance imaging.

Conclusions: Cocaine dependence and ELS were significantly and differentially associated with altered expression of individual personality traits and holistic personality profiles.

Poster #3

Tolerance and Cross-Tolerance among High-Efficacy Synthetic Cannabinoids JWH-018 and JWH-073 and Low-Efficacy Phytocannabinoid Δ^9-THC

William E Fantegrossi, Lirit N Franks, Tamara Vasiljevik, Paul L Prather.

Repeated administration of cannabinoid agonists has been shown to result in tolerance to several central and peripheral effects in laboratory animals, and to cellular effects observed *in vitro*. Intrinsic efficacy is known to modulate pharmacodynamic tolerance at several central receptor systems, but whether this phenomenon also applies to cannabinoid receptors has not been adequately explored. In these studies, daily injections of the high efficacy synthetic cannabinoids JWH-018 and JWH-073, or the low-efficacy phytocannabinoid Δ^9-THC were administered to mice previously prepared with radiotelemetry probes capable of simultaneously monitoring core temperature and locomotor activity. In separate groups of mice, the effects of JWH-018 and JWH-073 were assessed in subjects with or without a history of Δ^9-THC administration. Repeated administration of all three cannabinoids resulted in almost complete tolerance to hypothermic effects within 5 days, and when re-challenged with the same dose after a 14-day drug abstinence period, some degree of tolerance was still evident for all three cannabinoids. Interestingly, no tolerance to locomotor suppression was noted for any of the cannabinoids. Mice made tolerant to the hypothermic effects of Δ^9-THC after 4 daily administrations also exhibited near complete tolerance to the hypothermic effects of JWH-018 and JWH-073 on day 5, and in both cases, residual tolerance was still apparent after a 14-day drug abstinence period. Potential mechanisms for these observed *in vivo* effects were investigated *in vitro* using assays of CB1 receptor expression and function. These studies suggest that intrinsic efficacy at CB1 receptors is not a primary variable in eliciting tolerance to hypothermic effects in mice. However, most importantly, we propose that tolerant marijuana users may attempt to overcome diminished drug effects by escalating SCB dose, increasing the potential for serious adverse effects associated with use of these dangerous drugs of abuse. This work supported by RR020146 and RR029884.

Poster #8

Dextroamphetamine Withdrawal Paradigm in Methamphetamine Dependent Humans

Michael Mancino, Janette McGaugh, Jeff Thostenson, D. Keith Williams, Alison Oliveto

Treatment-seeking methamphetamine (METH) dependent individuals were enrolled in this 4-week, randomized, double-blind, placebo-controlled, pilot clinical trial examining the impact of abruptly stopping amphetamine administration in METH dependent individuals stabilized on oral d-amphetamine (DEX) on mood, sleep patterns, and thinking. Participants were admitted to a residential treatment facility, started on DEX during week 1 of the study to receive either DEX or placebo (PLA) during wks 2-3. All participants received PLA during week 4. Assessments were completed at least weekly during the study and included vital signs, mood, withdrawal and craving scores. Participant's desire for METH was lower in the DEX group compared to placebo. Methamphetamine withdrawal and Methamphetamine Selective Severity Assessment score also showed a trend toward being lower in the DEX compared to the PLA groups. Although there were significant decreases in heart rate between wks 1 and 2 in the PLA group, no significant changes in pulse were found in the DEX group. No significant differences were observed in blood pressure between groups or over time. To our knowledge, this is the first double blind, PLA-controlled trial for determining the pharmacologic effects of abruptly stopping amphetamine administration in METH dependent humans. These preliminary results suggest that this paradigm of amphetamine withdrawal may be useful in examining the efficacy of pharmacologic agents in alleviating early METH withdrawal symptoms. (Supported by NCRR grant RR020146)

Poster #7

Mediators of Response to Sertraline vs. Placebo among Recently Abstinent, Cocaine Dependent Patients

Alison Oliveto, Jeff Thostenson, Thomas R. Kosten, Michael Mancino

In order to optimize treatment outcomes with the dopamine reuptake inhibitor sertraline (SERT), data from two 12-wk, randomized, double blind, placebo-controlled clinical trials of SERT for preventing relapse among recently abstinent, cocaine dependent patients (N=126) were analyzed to determine mediators of treatment response. Participants resided at a residential treatment facility (wks 1-2) and randomized to receive either SERT alone (200 mg/day) or placebo. Participants transferred to outpatient treatment (TRU) at the start of their third week, continued to receive study medications or placebo (weeks 3-12) and participated in weekly individual cognitive behavioral therapy. Compliance with study protocol was facilitated by providing monetary compensation for attendance and for returning blister packs. Supervised urines were obtained thrice weekly. The primary outcome was relapse (i.e., 2 consecutive urines positive for cocaine). Logistic regression showed the odds ratio (OR) of the SERT group vs. the placebo group to be 0.64($p<0.0001$), making SERT-treated subjects significantly less likely to relapse than placebo subjects. The model also adjusted for several other covariates including: gender, age, current alcohol dependence diagnosis (ADD) and the interaction of treatment group and current ADD. Women were less likely to relapse than men (OR=0.45, $p<0.0001$). Older subjects were more likely to relapse than younger subjects (OR=1.06, $p=0.02$). ADD subjects were more likely to relapse than those who were not dependent (OR=3.45, $p=0.0002$). However, the ADD effect was moderated in SERT-treated subjects by the interaction term (OR=0.30, $p=0.0004$). Thus, participants who are women or younger may have better outcomes in a relapse model regardless of treatment. In addition, outcomes in ADD participants were more negative than non-ADD participants when receiving placebo, but not SERT. Overall, the results suggest that SERT improves outcomes relative to placebo, especially in those with comorbid ADD. (Supported by NIDA grant **P50 DA12762**)

Poster #4

Discovery of Long Acting Monoclonal Antibodies for Treating Methamphetamine Abuse

Michael Hambuchen, William Atchley, Melinda Gunnell, Sherri Woods, Eric Peterson, Brooks Gentry , Michael Owens

There are no approved medications to help patients recover from methamphetamine (METH) addiction. In animal models of METH use, anti-METH monoclonal antibodies (mAb) show promise as a method to block or reduce METH-induced pharmacological effects. These novel, biological medications could play a vital role in helping patients to achieve sustainable abstinence from METH use by serving as an in vivo, around-the-clock sentry against a patient's vulnerability to METH use. In these studies we showed how we discovered mAb medications and some of their potential benefits as long acting medications that keep METH away from sites of action in the brain.

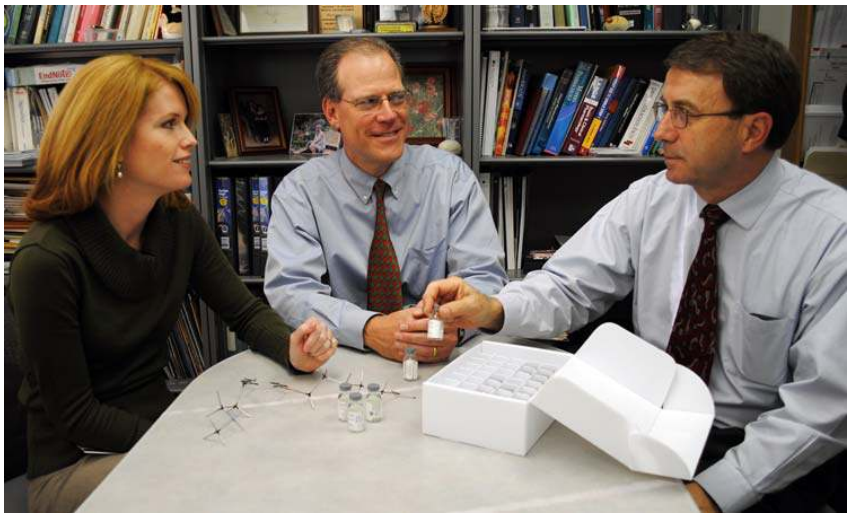
Our early studies revealed that some anti-METH mAbs get inactivated after administration to animals. This destroys their ability to reduce METH effects in the brain. By modifying the way we generate and test the antibodies, we have significantly improved the success of discovering mAbs with long lasting function (*e.g.*, several weeks).

To show the beneficial long-lasting effects of mAb medications, we tested our lead candidate in a one-month study in which the mAb was administered once a week for three weeks. During this time of mAb treatment, we also challenged the animals with multiple doses of METH to determine how the mAb reduced METH pharmacological effects. The results showed the mAb was still protecting the animals one month after the start of treatment (Funding by NIDA and TRI).

Poster #5

First Human Studies of an Anti-Methamphetamine Monoclonal Antibody

Misty Stevens, PhD, MBA, S. Michael Owens, PhD, W. Brooks Gentry, MD



Methamphetamine (METH) abuse causes serious medical, social, and economic harm in the USA and the world. However, to date, no medications are approved to treat METH addiction. In a collaborative effort between scientists at UAMS and InterveXion Therapeutics, an anti-METH specific antibody medication has been developed and tested in a human clinical trial (with non-drug using volunteers) for the first time. This antibody medication works by quickly binding METH in the blood and preventing the drug from rushing into the brain. Results from the clinical trial show that the antibody lasts a long time after a single dose, around three weeks, therefore dosing will be infrequent. Importantly, no serious adverse events related to study drug occurred during the course of the study suggesting that the treatment may be safe for use in larger populations. The next steps include a Phase 1b clinical trial, which would test the safety of the antibody medication in METH users. In addition, the effects of the antibody on METH kinetics will be studied as a preliminary assessment of efficacy in humans.

Poster #6

Preclinical Abuse Liability of Methoxetamine, an Emerging Arylcyclohexylamine Drug of Abuse

William E Fantegrossi, W. David Wessinger, Brenda M. Gannon, Andrew P. Norwood, William S. Hyatt, Jonathan Bauer-Erickson

In recent years, extensive internet availability of a range of “research chemicals” has lead to the emergence of new compounds as drugs of abuse, including arylcyclohexylamine analogues of the non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist phencyclidine (PCP). In this study, we compared one of the most prevalent of these compounds, methoxetamine (MXE), to the structurally similar arylcyclohexylamines phencyclidine (PCP), eticyclidine (PCE) and tenocyclidine (TCP) using complementary rodent models. First, PCP was established as a discriminative stimulus in rats. Once discrimination was established, substitutions were performed with various doses of PCP, eticyclidine (PCE), tenocyclidine (TCP) or the negative control compounds morphine and JWH-018. PCP, MXE, PCE and TCP dose-dependently and fully substituted for the PCP training dose, while morphine and JWH-018 did not. Next, these same rats were implanted with osmotic mini-pumps to elicit PCP dependence. Suppression of response rates in a food-maintained operant task was used as an index of withdrawal when the pumps were removed after 10 days. Increasing doses of MXE restored normal behavior in PCP-dependent rats. A separate group of rats was trained to self-administer intravenous PCP, and substitutions with various doses of MXE were performed. The reinforcing effects of MXE were weaker than those of PCP. Finally, mice were implanted with biotelemetry probes to simultaneously assess core temperature and locomotor activity in response to increasing doses of PCP, PCE, TCP or MXE. All compounds produced locomotor stimulant effects and elicited hypothermia. In all assays, MXE was more potent than PCP. These results suggest that novel arylcyclohexylamine drugs of abuse are likely to be more potent than human users of these emerging drugs might expect, perhaps leading to overdose if they base their doses on PCP. This work supported by RR020146, RR029884, and by ASPET SURF awards to JBE.