



Showcase of Medical Discoveries

A Focus on Opioids



Wednesday
November 14, 2018

***A Wine & Cheese Reception Featuring
UAMS Investigators Discussing their
Research and Discoveries.***

Winthrop P. Rockefeller Cancer Institute
10th Floor Rotunda



Poster #1

Management of Infants Exposed in utero to Opioids



Jeannette Lee, Ph.D. and Jessica Snowden, M.D.

One of the consequences of the opioid crisis is that an increasing number of infants are exposed *in utero* to opioids and developing neonatal opioid withdrawal syndrome (NOWS). There is no standard approach to the care of mothers and infants with NOWS. Infants with NOWS utilize significant health care resources and social services.

UAMS serves as the Data Coordinating and Operations Center (DCOC) for the IDeA States Pediatric Clinical Trials Network (ISPCTN), a component of the NIH-funded Environmental Influences on Child Health Outcomes program. The Network includes 17 clinical awardee sites in the IDeA states which have been disproportionately affected by the opioid crisis. The ISPCTN has partnered with the Neonatal Research Network (NRN), another NIH funded multicenter clinical trial network, to address the issue of management of infants exposed *in utero* to opioids.

ISPCTN and NRN are involved in the following ongoing collaborative activities: a survey on NOWS treatment practices among NICUs and delivery units; a chart review of demographic characteristics, maternal and infant drug exposures, and pharmacologic and non-pharmacologic management of NOWS infants; and the plans for two interventional clinical trials. The surveys will summarize current practices; the trials will test patient-level and site-level interventions.

Poster #12

AR IMPACT: Arkansas Improving Multi-Disciplinary Pain Care Team



Masil George, MD, Teresa Hudson, PharmD, PhD, Corey Hayes, PharmD, MPH, Shona Ray-Griffith, MD, Johnathan Goree, MD, Leah Tobey, PT, DPT, Micheal Cucciare, PhD, Richard Smith, MD

In 2013 the National Institute on Drug Abuse reported that Arkansas providers wrote 117.5 opioid prescriptions for every 100 persons (approximately 3.5 million prescriptions). In the same year, the average U.S. rate was 79.3 opioid prescriptions for every 100 persons. Since then, several steps have been taken to curb the opioid epidemic and reduce opioid prescribing in Arkansas. One of the key challenges in changing opioid prescribing is to provide clinicians with evidence-based information about other strategies for pain management. Therefore, in mid-2018 the AR-IMPACT team was created.

AR-IMPACT is a multidisciplinary team that includes expertise in addiction, pharmacy, psychology, physical therapy, pain management and general medicine/geriatrics/palliative care. AR-IMPACT provides a case-based seminar every Wednesday at noon via statewide televideo broadcast. It is available to anyone with the ability to join the presentation electronically. Those on the UAMS campus may join the team in room 136 in the PRI building. Continuing education credits are available. Each one-hour session includes an evidence-based presentation lasting 15-20 minutes followed by a case-based discussion. Participants are encouraged to offer their own cases and insight into pain management strategies.

Poster #11

Evidence Based Quality Improvement (EBQI) for Development and Implementation of Community Pharmacist-Initiated Prescribing and Dispensing of Naloxone



Mary Thannisch, Benjamin Teeter, PhD, Geoffrey Curran, PhD, Duane Jones, BSPHarm, Bradley Martin, PharmD, PhD, Nickolas Zaller, PhD

EBQI is rooted in the principles of participatory research and brings together clinical and implementation experts with providers and decision makers to adapt evidence-based practices. This study utilized EBQI to adapt protocols/materials developed by colleagues at Brown University and successfully tested in 400+ pharmacies. Four 2-hour long EBQI sessions were attended by the UAMS research team, our partner pharmacy's (Harp's) district manager, 2 pharmacy managers, 2 community informants, and the Arkansas Pharmacists Association's Vice President for Practice Innovation. Strategies to overcome potential implementation barriers were selected from a list created by the Expert Recommendations for Implementing Change (ERIC) study. An EBQI summary template was used to document the process.

EBQI resulted in selection and adaptation of four posters and one pamphlet. A second pamphlet and a vial cap sticker were also developed. Scripts for identification of and conversations with high-risk patients were adapted and protocols established. Analysis of summary templates is ongoing. Preliminary results suggest EBQI may be beneficial for adaptation of evidence-based interventions for use in the community pharmacy setting.

Poster #2

The Effects of P-glycoprotein Inhibition on Norbuprenorphine-induced Neonatal Abstinence Syndrome (NAS)



Paloma Salazar, William T Higgins, Lisa K Brents

Treating pregnant, opioid-addicted women with the opioid buprenorphine improves mother-child outcomes, but can cause neonatal abstinence syndrome (NAS), a potentially life-threatening withdrawal syndrome newborns often develop following chronic prenatal exposure to opioids. NAS severity is independent of maternal buprenorphine dose, suggesting that inter-individual variance in the pharmacokinetics of buprenorphine may influence NAS. We previously showed that prenatal exposure to the major active metabolite of buprenorphine, norbuprenorphine (NorBUP), can induce NAS. NorBUP is a substrate of the highly polymorphic placental efflux transporter P-glycoprotein, which transports its substrates from fetal to maternal circulation. We tested the hypothesis that **inhibiting P-glycoprotein increases NorBUP-induced NAS severity**. We administered a subthreshold dose of NorBUP or vehicle to pregnant rats from gestation day (GD) 9 until post-delivery and treated them twice daily with the p-glycoprotein inhibitor Elacridar or vehicle on GD18-21. After delivery, pups were observed for precipitated withdrawal signs following administration of naltrexone or saline. NorBUP and Elacridar together, but not individually, increased naltrexone-precipitated withdrawal signs, providing the first evidence that P-glycoprotein activity can substantially modulate the effects of NorBUP on the fetus and may therefore contribute to the uncoupling of maternal buprenorphine dose and NAS severity.

Poster #3

Morphine 6-O-Sulfate is a novel mixed μ/δ Opioid Therapeutic for Diabetic Neuropathy: Pharmacology, Pharmacokinetics, and Blood Brain Barrier Permeability



Jai Shankar K.Yadlapalli, Zaineb Albayati, Benjamin M Ford, Amit Ketkar, Anqi Wan, Narasimha Penthala, Robert Eoff, Paul L Prather, Howard Hendrickson, Maxim Dobretsov, and Peter A Crooks

Treatment of diabetic neuropathic pain (DNP) still remains a vexing problem. Various drugs, including opioids, have limited efficacy and undesirable side effects. Hence, development of new compounds for treatment of NP that lack opioid side-effects, including tolerance, has become a high priority. Morphine 6-O-sulfate (M6S) appears to be one such promising agent. This study compares the analgesic efficacies of morphine (MOR) and M6S in a rat model of DNP and in naïve rats. Diabetes was induced in male Sprague-Dawley rats with streptozotocin (65 mg/kg i.p.). Paw pressure, pinprick sensitivity and hot plate withdrawal thresholds (PPT, PST and HPT) were measured at various time points and doses after drug injection. Cell culture assays were performed in Chinese hamster ovary cells transfected with human mu- or delta-opioid receptors. HPLC-DAD stability studies were performed *in vitro* in various pH buffers. Pharmacokinetic parameters were studied after i.v., i.p. and oral administration. M6S was 3-3.5-fold more potent compared to MOR in both non-diabetic and diabetic animals. Also, M6S demonstrated delayed development of tolerance over morphine in all pain modalities tested. Our studies demonstrate that M6S activates both mu opioid- and delta opioid-receptor pain control pathways, and appears to be a superior drug compared to morphine.

Poster #10

Development of G-protein Biased Cannabinoid Receptor Agonists as Potential Alternatives to Opioid Treatment of Chronic Pain



Paul L. Prather, Narsimha R. Penthala, William E. Fantegrossi, and Peter A. Crooks

Opioids are prescribed to treat severe pain, but can result in death from overdose and/or addiction if taken for long periods of time. In contrast, 9 D-tetrahydrocannabinol (9 D-THC), the active ingredient in medicinal *cannabis*, also relieves pain with fewer dangerous adverse effects. Synthetic drugs developed to mimic actions of 9 D-THC (*e.g.*, cannabinoids) bind to cannabinoid type-1 (CB₁Rs) and type-2 (CB₂Rs) receptors and are potential therapeutic candidates for acute and chronic pain. Activation of CBRs produces a bifurcation of signaling: G-protein activation, responsible for analgesia and other therapeutic effects; while β_2 -arrestin recruitment may contribute to adverse effects upon short-term use, and tolerance following prolonged use. Therefore, biased CBR agonists that preferentially activate G-proteins relative to β_2 -arrestin recruitment may be safer analgesics than currently available unbiased agonists such as 9 D-THC. Our group has recently developed a novel class of indole quinuclidinone (IQD) CBR ligands of which two analogs are dual-hybrid compounds binding non-selectively to both types of CBRs. Specifically, these analogs act as G-protein biased agonists at CB₁Rs, while exhibiting unbiased agonist activity at CB₂Rs. Lead compound (PNR-4-20) produces analgesia in mice with reduced tolerance following prolonged treatment relative to 9 D-THC. Compounds in this class may provide analgesia with fewer adverse effects than either 9 D-THC or opioids.

Poster #9

In vivo Dependence Liability Assessment of Novel Fentanyl Analogues: Science to Guide Drug Policy



Kyle R. Urquhart, Saki Fukuda, Jyoti Gogoi, Timothy Flanigan, Takato Hiranita and William E. Fantegrossi

The emergence of fentanyl analogues as drugs of abuse raises concern regarding their dependence liability. Following prolonged opioid administration, physical dependence leads to increased use, which facilitates the development of tolerance and the dangers of overdose. In animal models, opioid dependence can be inferred by assessing signs of withdrawal, with vertical jumping being the most sensitive and easily quantified in the mouse. In this study, we aimed to characterize the abuse liability of fentanyl, morphine, and six fentanyl analogues by generating a therapeutic index for dependence. Compounds with lower therapeutic indices would be considered to have greater dependence liability and therefore greater abuse potential. To determine analgesic effects, we used a warm-water tail withdrawal procedure using both 50°C and 55°C water, while dose-effect curves for withdrawal jumps elicited by naloxone in fentanyl and fentanyl analogue dependent mice were generated starting with the lowest fully analgesic dose and increasing in half-log units. Fentanyl and all analogues were fully effective analgesics in both 50°C and 55°C water, and all drugs induced dependence evidenced by naloxone-elicited jumping. Differences in potencies across these two endpoints allowed determination of potency ratios ($ED_{50\text{-analgesia}}/ED_{50\text{-jumps}}$) to rank these drugs in order of dependence liability, and provide valuable insight into our nation's opioid crisis, which is currently fueled by fentanyl and emerging fentanyl analogues.

Poster #4

Improving Opioid Use Disorder Treatment Outcomes with the L-type Calcium Channel Blocker Isradipine



A.H. Oliveto, J. McGaugh, J.B. Guise, J. Thostenson and M.J. Mancino

The feasibility and efficacy of the L-type calcium channel blocker isradipine to improve outcomes during buprenorphine stabilization/detoxification were explored in an 8-wk, double blinded, placebo-controlled, randomized, out-patient trial. Opioid-dependent subjects were randomized to receive isradipine or placebo, inducted onto buprenorphine (12 mg/day) during wk 1 and onto isradipine at up to 10 mg BID or placebo during wks 1-4. [Data from the 10-day buprenorphine taper during wks 5-6 and isradipine taper during wks 7-8 will not be presented.] Twenty-five participants entered the study proper (isradipine, N=11; placebo, N=14), 16 of which completed isradipine induction. Six subjects were discontinued due to vitals being outside dosing parameters. Baseline characteristics, retention and opioid withdrawal ratings did not differ between groups. During the buprenorphine/isradipine induction, isradipine significantly decreased opioid-positive urines over time as well as craving measures relative to placebo. Vitals taken pre and 2 hrs post the first scheduled isradipine dose and each scheduled dose increase differed by medication group: post-blood pressure measures generally decreased and increased relative to pre-blood pressure measures in the isradipine- and placebo-treated subjects, respectively. Thus, isradipine may improve initial treatment outcomes during BUP stabilization, but likely the low vital signs typically observed in this population would contraindicate use.

Poster #5

A Survey of Treatment Preferences for Opioid Use Disorder

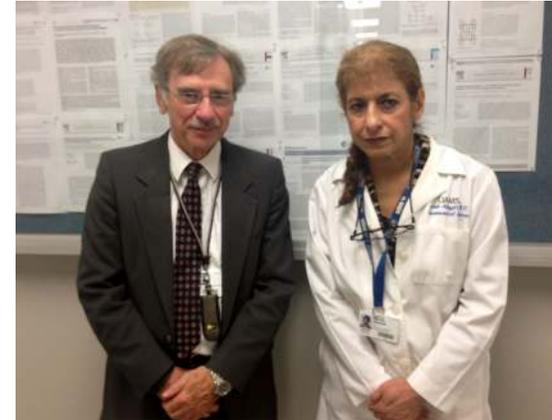


R. Nahata, M.J. Mancino, J. Thostenson, A. Oliveto

Opioid use disorder (OUD) has reached a crisis point, particularly with the rise in prescription opioid (PO) abuse. PO users tend to differ from heroin users (e.g., younger, less OUD treatment history, greater social stability) and may not prefer long-term maintenance treatment with opioid agonists methadone (MTD) or buprenorphine (BUP), but acceptability of opioid antagonist naltrexone (NTX) treatment following opioid detoxification is also unclear. This survey gathered preliminary data on the feasibility of using injection NTX therapy among 100 opioid users undergoing health screening to determine study eligibility for an ongoing study. Twenty-six, 16, 16, 1 and 0 reported prior treatment episodes of detoxification, BUP, MTD, oral NTX and injection NTX, respectively. Ninety and 71% were interested in a study involving oral and/or injection NTX treatment, respectively. Significantly more of those interested in injection NTX had prior opioid agonist maintenance treatment episodes relative to those uninterested ($p < 0.03$). Those preferring injection NTX therapy showed more interest in this therapy ($p < 0.0001$) and less interest in BUP treatment ($p < 0.03$) than those not preferring injection NTX. Results suggest that those with failed agonist maintenance treatment history are more likely to consider injection NTX, indicating it may be optimal as a second-line OUD treatment.

Poster #8

A Comparison of the Antinociceptive Effects of ZZ204G, an $\alpha 9\alpha 10$ nAChRs Antagonist and Morphine in a Rodent Model



Anqu Wani, Jai Shankar K. Yadlapalli, E. Kim Fifer, Maxim, Dobretsov, Zaineb Albayati and Peter A. Crooks

Treatment of multimodal chronic pain remains a problem because of differential sensitivity of different types of pain to a given treatment and side effects of existing analgesics (opioids, NSAIDs, etc.). Although the real target remains elusive, some selective $\alpha 9\alpha 10$ nicotinic acetylcholine receptor (nAChR) antagonists (α -conotoxins and small non-peptide molecules) were identified as promising and well-tolerated pharmaceutical tools for pain treatment. ZZ204G, a *tetrakis*-quaternary ammonium salt, potently and selectively blocks rat $\alpha 9\alpha 10$ nAChRs expressed in *Xenopus* oocytes ($IC_{50} = 0.65$ nM). In this study, ZZ204G was synthesized and studied in several evoked pain tests in rats. Morphine (MOR) was used as a reference standard. To further discover the potential clinical application of ZZ204G, a chronic treatment of ZZ204G was studied during a 9-day course.

Poster #7

In vivo Abuse Liability Assessment of Novel Fentanyl Analogues: Science to Guide Drug Policy



William E. Fantegrossi, Kyle R. Urquhart, Saki Fukuda, Jyoti Gogoi, Timothy Flanigan and Takato Hiranita

Abuse of opioids carries risks of dependence, addiction and overdose, and the emergence of novel high potency fentanyl analogues on the illicit market is currently fueling the so-called “opioid crisis” in the US. Thorough characterization of abuse-related effects of these compounds may aid in regulatory efforts to curtail their availability. In these studies, we characterized dose- and time-dependent effects of fentanyl, morphine, and six fentanyl analogues on locomotor activity in the mouse, and determined the potency and effectiveness of the fentanyl analogues to substitute for morphine in a rat model of subjective effects. Challenges with the opioid antagonists naloxone or naltrexone were employed to confirm opioid receptor dependent mechanisms for observed effects in both assays. All opioids effectively and dose-dependently increased locomotor activity in the mouse, but decreased ambulatory speed. All fentanyl analogues were more potent than morphine in the mouse. In rats, all drugs dose-dependently and fully substituted for morphine in the discrimination task, and suppressed rates of responding as well. In all cases, opioid effects were blocked by antagonist administration. Data from these experiments allows drugs to be ranked in order of potency to induce abuse-related effects, and provide important information on the likelihood of these drugs to be abused in humans.

Poster #6

Community Pharmacists’ Perceptions of their Role in the Opioid Epidemic



Benjamin Teeter, PhD, Geoffrey Curran, PhD, Bradley Martin, PharmD, PhD, Patricia Freeman, RPh, PhD, Karen Drummond, PhD, Katharine Bradley, MD, and Mark Edlund, MD, PhD

Opioid use disorder continues to be a major public health concern. Little is known regarding pharmacists’ perceptions of their role in the opioid epidemic. The objective of this study was to determine pharmacists’ perceptions of their patients’ overdose risk, their willingness to provide screening and interventions for opioid and other substance use disorders at the point of care, and their participation in prescribing and dispensing naloxone.

Findings suggest that pharmacists are concerned about overdose, but those concerns are moderated by beliefs that the majority of people overdosing are illicit users and not their patients taking prescribed opioids as directed. Pharmacists in the sample ranged widely in their levels of interest in conducting screenings or interventions to reduce the risk of overdose. Few reported ever referring patients to treatment for addiction. Although they feel referral to treatment is within their scope of practice, they worry about offending their patients – especially those that they do not have an established relationship with. Pharmacists reported needing education on available patient resources as to who may show signs of addiction. Pharmacists in the sample reported seeing very few prescriptions from physicians for naloxone. Although many pharmacists have recently gained the ability to dispense naloxone without a physician-written prescription, most in our sample reported few instances of doing so.

Community pharmacists could be more involved in/intervening around opioid and other substance use issues, but they need additional education, resources, and implementation support to be effective. In the short term, increased attention to naloxone provision in community pharmacies could positively impact overdose risk.