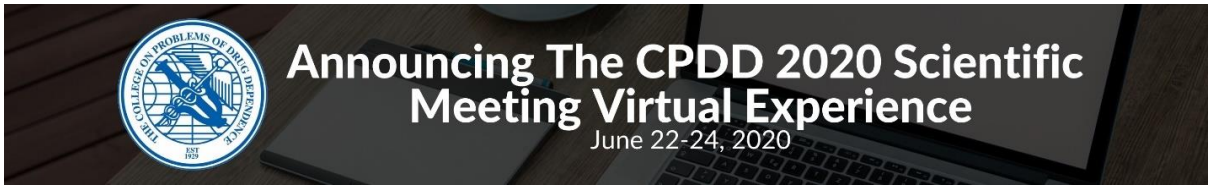

Late-Breaking Presentation Session I

3:30 p.m. - 4:30 p.m.

PERCEIVED IMPACTS OF COVID-19 ON SUBSTANCE USE AMONG PEOPLE WITH HIV/AIDS: PERSPECTIVES OF HIV/AIDS SERVICE ORGANIZATIONS ACROSS THE UNITED STATES

Bryan Garner[*1], Brittany Zulkiewicz[1], Hannah Knudsen[2]*

[1]RTI International, [2]University of Kentucky

Abstract Detail: Human
Drug Category: Polydrug (i.e. Use of more than one drug combination)
Topic: HIV/Immune
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Given the major societal disruptions of the COVID-19 pandemic and its accompanying stressors, concerns are growing that the pandemic is increasing substance use, particularly among individuals with chronic conditions, such as HIV/AIDS. This study aimed to describe the perceived impacts of COVID-19 on substance use among clients served by HIV/AIDS service organizations (HSOs) in the United States and whether those impacts also increase the need for substance use disorder (SUD) treatment integration in these organizations.
Methods: In April 2020, key staff members from 253 HSOs across the United States completed an online survey focused on the HSO's capacity to provide substance use treatment services to clients with SUDs. Survey items measured perceptions of the impact of the COVID-19 pandemic on: (a) their clients' substance use and (b) increasing the need for the HSO to offer substance use treatment services to clients with SUD, using a scale from 0 representing 'Not at all' to 3 representing 'To a great extent.'
Results: Overall, 57% (n=143) of HSOs reported providing substance use services as part of their service offerings. The average perceived impacts of COVID-19 on clients' substance use was 2.3 (SD=0.7), was 2.2 (SD=0.7) for increasing the prevalence of SUDs among the HSO's clients, and was 2.1 (SD=0.8) for increasing the need for the HSO offer effective substance use treatment interventions. HSOs currently lacking substance use services reported lower perceived need to offer effective treatment interventions because of COVID-19 (mean=2.0, SD=0.9) than HSOs that currently offer substance use services (mean=2.3, SD=0.7, p=.002).
Conclusions: From the perspective of HSOs, COVID-19 is likely to increase substance use and the prevalence of SUDs among clients served by their organizations. Increases in the prevalence of SUDs due to COVID-19 raise the urgency of integrating SUD interventions into HSOs across the United States.

BUPRENORPHINE DOSE AND PHYSICIAN, CLINIC AND PATIENT ENGAGEMENT IN THE TREATMENT OF OPIOID DEPENDENCE

Andrew Bergen[*1], James Baurley[2], Carolyn Ervin[2], Christopher McMahan[3], Joe Bible[3], Randall Stafford[4], Seshadri Mudumbai[5], Andrew Saxon[6]*

[1]Oregon Research Institute, [2]BioRealm, LLC, [3]Clemson University, [4]Stanford University, [5]Veterans Affairs Palo Alto Health Care System, [6]Veterans Affairs Puget Sound Health Care System

Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Treatment
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Efficacy of buprenorphine for treatment of opioid dependence is established. The influence of physician, staff and patient engagement in treatment have not previously been evaluated together with buprenorphine dose. Our hypothesis was that both dose and treatment engagement are associated with illicit opioid usage.
Methods: We selected participants from six buprenorphine efficacy and safety trials from NIDA's Data Share database. Treatment and opioid usage variables were derived from daily logs. The treatment variables included buprenorphine dosage (mg buprenorphine per day), adaptive dose (whether the daily dose could be adjusted by the physician), clinic visit (whether the patient attended clinic), and time in trial (trial day urinalysis occurred). To acknowledge their temporal relevance, these treatment variables were discounted by 50% each day (time-weighted). Opioid use events were defined by either self-report or positive urine testing. After exclusions, 3,022 participants randomized or enrolled in buprenorphine treatment for opioid dependence (mean (SD) age 36.1 (9.8) years, 33% female, 66% White, 16% Hispanic, 14% Black), were analyzed using a generalized linear mixed model with treatment variables and participant covariates.
Results: All treatment variables were significantly ($p < 0.001$) protective against illicit opioid use. Dosage and whether the clinician could modify the dosage had stronger effects than time-in-trial clinic visit. All treatment variables were novel predictors of the outcome. Significant ($p < 0.001$) participant covariates included several sociodemographic variables, and heroin use history, mode of heroin use and sedative use history.
Conclusions: Using publicly available trial data, we identified four novel treatment variables that were protective ($p < 0.001$) against illicit opioid use. After buprenorphine dose, treatment communication and engagement were the most important factors. While additional research may further elucidate mechanisms, these findings provide best prescribing practices, as well as supporting efforts to invest in patients' clinical experience.

FENTANYL-INDUCED CHANGES IN BRAIN ACTIVITY IN AWAKE NONHUMAN PRIMATES

Sarah Withey[*1], Lei Cao[2], Fernando de Moura[1], Kenroy Cayetano[1], Michael Rohan[1], Jack Bergman[1], Stephen Kohut[1]*

[1]McLean Hospital, Harvard Medical School, [2]McLean Hospital

Abstract Detail: Animal Study
Drug Category: Opiates/Opioids
Topic: Imaging
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Functional magnetic resonance imaging (fMRI) is a powerful in vivo tool that can be used to assess changes in opioid-induced brain activity at different stages of addiction. However, the direct pharmacological effects of opioids may be confounded by anesthetic agents required to maintain static posture for image acquisition. To avoid this complication, the present fMRI study was conducted to determine the effects of fentanyl in awake nonhuman primates.
Methods: Four adult male squirrel monkeys were gradually acclimated to awake scanning procedures. In subsequent 30-min fMRI sessions (9.4 Tesla, 1mm resolution, 1.5s TR), a dose of fentanyl that reliably maintains self-administration (1μg/kg) was delivered intravenously 10 mins into the recording sequence. The effects of fentanyl on patterns of brain activity were then assessed using: (1) an empirically-derived pharmacological regressor (phMRI) to elucidate fentanyl-induced patterns of neural activation and (2) a seed-based approach centered in the bilateral n. accumbens (NAc) to determine alterations in functional connectivity after fentanyl administration.
Results: Fentanyl produced a functional inhibition of activity in multiple brain regions known to be involved in the reward-related effects of opioid agonists, including the cingulate cortex, nucleus accumbens, and thalamus. However, functional connectivity from the NAc, which decreased to regions involved in motoric and/or cognition-related behavior (e.g., thalamus, orbitofrontal, prefrontal, and cingulate cortices) increased to striatal regions (e.g., caudate and putamen) that also have been implicated in reward processes.
Conclusions: Results suggest that this fMRI approach, using awake nonhuman primates, can be utilized to investigate changes in neural circuitry following opioid administration and, perhaps, to investigate medication-related changes in opioid-induced neural activity.

SEX DIFFERENCES IN THE AVERSIVE EFFECTS OF METHYLONE

Hayley Manke[*1], Katharine Nelson[1], Anna Vlachos[1], Jacob Bailey[1], Karina Maradiaga[1], Tania Weiss[1], Kenner Rice[2], Anthony Riley[1]*

[1]American University, [2]National Institute of Drug Abuse, National Institutes of Health

Abstract Detail: Animal Study
Select Drug Category: Club/Designer Drugs
Topic: Sex Differences
Abstract Category: Original Research
Designation: B.A.

Abstract: Aim: While methylone's rewarding effects have been well characterized, little is known about its aversive effects, a property that modulates the intake of abused drugs. In this context, this study investigated the aversive effects of methylone as assessed by taste avoidance conditioning, hyperthermia and hyperactivity).

Methods: 35 male and 31 female Sprague-Dawley rats were given access to a saccharin solution followed by an intraperitoneal injection of methylone (0, 5.6, 10 or 18 mg/kg) every 4th day for a total of five trials. Following drug washout, subjects were randomly injected with various does of methylone and monitored for temperature by subcutaneous probes for 8 hours). Following a second washout, subjects were randomly injected with methylone or vehicle and motor activity (gross and stereotypes) was monitored for 1 hour.
Results: Given different baselines for male and female subjects, statistical analyses for each assessment were done separately for males and females using mixed model ANOVAs ($p < 0.05$). Methylone induced significant dose-dependent taste avoidance at all doses with females requiring an additional trial to acquire the aversion (all ps < 0.05). Males displayed dose- and time-dependent hyperthermia. Females initially displayed dose- and time-dependent hypothermia followed by hyperthermia (at lower doses than males). Males and females displayed time- and dose-dependent hyperactivity with males displaying faster onset and females displaying longer duration. Males and females displayed time- and dose-dependent stereotypies with no consistent differences.
Conclusions: These findings parallel prior work with related bath salts, e.g., MDPV and α-PVP, although the specific mechanisms of action for these compounds differ. Given that drug intake appears to be a function of the balance of its rewarding and aversive effects, understanding both of these effects of methylone and the factors impacting them may provide insight into predicting its abuse potential.

VARENICLINE-ASSOCIATED CHANGES IN STRIATAL DOPAMINE D2-TYPE RECEPTOR AVAILABILITY: ASSOCIATIONS WITH IMPULSIVITY AND CRAVING IN STIMULANT USERS

Megan McClintick[*1], Dara Ghahremani[1], Andrew Dean[1], Kaitlin Kinney[1], Elizabeth Rizor[1], Tarannom Mahmoudie[1], Larissa Mooney[1], Mark Mandelkern[2], Edythe London[1]*

[1]University of California Los Angeles, [2]Veterans Administration of Greater Los Angeles Health System

Abstract Detail: Human
Drug Category: Stimulants
Topic: Substance Use Disorder
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Stimulant use is associated with higher self-reported impulsivity and risk-taking, striatal dopamine D2-type receptor (DRD2/3) deficits. Varenicline produces striatal upregulation in rats and improvements in cognitive function in humans, but its efficacy as medication to target dopamine transmission, impulsivity and risk-taking in humans has not been assessed.
Methods: Twelve stimulant users (11 men / 1 woman) completed [18F]-fallypride Positron Emission Tomography scans and self-report measures of impulsivity (Barratt Impulsiveness Scale), risk-taking (Domain-Specific Risk-Taking Scale), and craving (Methamphetamine Craving Questionnaire – Brief or Cocaine Craving Questionnaire – Brief) for their stimulant of choice (4 cocaine / 8 methamphetamine) before (Time 1) and after (Time 2) taking oral varenicline or placebo in a double-blind protocol. Participants met criteria for Stimulant Use

Disorder (DSM-5 MINI) and received study medication [Arm A, n = 7; Arm B, n = 5] for 21 days during inpatient treatment. Groups remain blinded.
Correlational analyses controlling for age tested for associations between changes in self-report measures and striatal DRD2/3 BPND within each Arm. Repeated measures ANOVA and Wilcoxon Signed-Rank Tests assessed changes in DRD2/3 BPND and self-report from Time 1 to Time 2.

Results: Striatal DRD2/3 BPND and self-report measures did not significantly differ from Time 1 to Time 2 in either arm. Both arms exhibited increases in striatal DRD2/3 BPND from Time 1 to Time 2, with Arm A increases exceeding those of Arm B by 1.5%-13.2%. Preliminary findings suggest that in Arm A, increases in striatal DRD2/3 BPND negatively correlated with decreases in impulsivity (putamen: $r = -0.88$, $p = 0.05$; nucleus accumbens: $r = -0.86$, $p = 0.06$).
Conclusions: The heightened impulsivity but not craving or risk-taking observed in chronic stimulant users may be tightly linked to striatal D2-type receptor BPND. Moreover, subchronic treatment with varenicline may increase striatal DRD2/3 BPND to decrease impulsivity.

ABUSE LIABILITY ASSESSMENT OF JL ELECTRONIC NICOTINE DELIVERY SYSTEM (ENDS) IN TWO NICOTINE CONCENTRATIONS COMPARED TO USUAL BRAND CIGARETTE, NICOTINE GUM AND A COMPARATOR ENDS

Nicholas Goldenson[1], Jack Henningfield[2], August Buchhalter[2], Mark Rubinstein[1], Erik Augustson[1], Jack Henningfield[2]*

[1]JUUL Labs, Inc., [2]Pinney Associates, Inc.

Abstract Detail: Human
Drug Category: Nicotine/Tobacco
Topic: Substance Use Disorder
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: To assess the abuse liability of JL Electronic Nicotine Delivery System (ENDS; JUUL Labs, Inc.) in 5.0% and 3.0% nicotine concentrations compared to usual brand (UB) cigarette, a comparator ENDS, and 4 mg nicotine gum, with measures of nicotine uptake (pharmacokinetic [PK] parameters) and subjective effects under acute ad libitum use conditions.
Methods: Adult smokers (N=146; 45.9% female; mean age=41.3) were randomized to a within-subjects cross-over sequence for five study test products: (1) JL ENDS 5.0% nicotine; (2) JL ENDS 3.0% nicotine; (3) UB cigarette; (4) 4 mg mint nicotine gum; (5) comparator ENDS (Vuse Alto 5.0%). One product was tested per study day by ad libitum administration (5 minutes for ENDS and UB cigarette; 30 minutes for gum). After each product administration, nicotine PK and subjective effects were assessed.
Results: UB cigarette resulted in the highest mean maximum plasma nicotine concentration (Cmax-BL [ng/mL]; 21.70) followed by the comparator ENDS (14.58), JL ENDS 5.0% (9.86), JL ENDS 3.0% (7.42) and nicotine gum (6.26). Similarly, UB cigarette had the significantly highest rate of plasma nicotine rise (ng/mL per minute) and total nicotine exposure (area under curve [AUC0-60-BL]); the comparator ENDS was significantly greater than both JL ENDS products (5.0% and 3.0%). Mean time to maximum plasma nicotine concentration (Tmax) among the UB cigarette, JL and comparator ENDS (7.23-8.67 minutes) were significantly

faster than nicotine gum (43.39 minutes). Ratings of product appeal and satisfying effects were significantly highest for the UB cigarette; nicotine gum was rated lowest.
Conclusions: These results suggest that the abuse liability of the JL ENDS, both 5.0% and 3.0%, is: (1) substantially lower than the UB cigarette; (2) somewhat lower than the comparator ENDS; (3) higher than nicotine gum; and (4) the abuse liability of the JL ENDS 5.0% is somewhat higher than the JL ENDS 3.0%.

PILOT RANDOMIZED CONTROLLED TRIAL OF EXENATIDE COMBINED WITH NICOTINE PATCH TO PROMOTE SMOKING CESSATION AND PREVENT WEIGHT GAIN

*Luba Yammine**[1], Charles Green[1], Thomas Kosten[2], Robert Suchting[1], Constanza deDios[1], Christopher Verrico[2], Joy Schmitz[1]*

[1]The University of Texas Health Science Center at Houston, [2]Baylor College of Medicine

Abstract Detail: Human
Drug Category: Nicotine/Tobacco
Topic: Substance Use Disorder
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Cigarette smoking remains the leading cause of preventable morbidity and mortality. For many smoker's post-cessation weight gain (PCWG) is a major obstacle to quitting; however, first-line smoking cessation treatments have a minimal impact on PCWG. Glucagon-like peptide-1 (GLP-1) agonists are FDA approved medications for type 2 diabetes and obesity that, in preclinical models, attenuate the reinforcing effects of nicotine and other abused drugs. We determined the efficacy of a GLP-1 agonist extended-release exenatide combined with the nicotine patch for smoking cessation and prevention of PCWG.
Methods: This double-blind, placebo-controlled trial randomized 84 prediabetic and/or overweight, treatment-seeking smokers in a 1:1 ratio to receive either exenatide, 2 mg subcutaneously once weekly (EXE) or placebo (PLC). All participants received nicotine patches (21 mg). Abstinence (expired CO level ≤5 ppm) and weight outcomes were assessed at the end of treatment (week 6). Generalized linear modeling was used to statistically evaluate each outcome. Bayesian inference was used to quantify the probability that the effect of treatment was greater or less than zero. Abstinence (vs. non-abstinence) was modeled as a function of treatment condition via the binomial distribution. Weight was modeled as a function of treatment condition, controlling for baseline weight, via the lognormal function.
Results: We found a 7.7% greater probability of abstinence favoring EXE (56.4%) over PLC (48.7%), corresponding to a 75.4% Bayesian posterior probability of this effect being greater than zero. Among those who quit smoking, EXE was associated with a 6.6 pound lower weight at week 6 compared to PLC (-3.33%, [-7, 49%, 0.98%]), corresponding to a 94.1% Bayesian posterior probability that this effect was less than zero.
Conclusions: Exenatide improved abstinence above and beyond standard nicotine patch and reduced PCWG. Larger studies of longer duration are needed to confirm these findings.

IDENTIFICATION OF DISTINCT LATENT NEURODEVELOPMENTAL PROFILES IN THE ADOLESCENT BRAIN AND COGNITIVE DEVELOPMENT STUDY

Sarah Lichenstein[*1], Corey Roos[1], Brian Kiluk[1], Kathleen Carroll[1], Patrick Worhunsky[1], Katie Witkiewitz[2], Sarah Yip[1]*

[1]Yale University School of Medicine, [2]University of New Mexico

Abstract Detail: Human
Drug Category: Other, Risk for problem substance use
Topic: Imaging
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Neurodevelopmental models of risk for addiction presume that, at the population-level, there exist subgroups of individuals with similar patterns of neural function and development, and that these subgroups contribute to vulnerability to substance use disorders. However, the presence of neurodevelopmental subgroups has not been empirically assessed in a large sample.
Methods: Neurodevelopmental profiles were identified via latent profile analyses (LPA) of fMRI data from 6,757 individuals in the ABCD Wave 1 data release who completed the Monetary Incentive Delay Task, the Stop Signal Task, and the Emotional N-Back task. Data were randomly split into model training and model testing samples and the optimal profile solution from the training data was applied to the testing data.
Results: LPAs in the training sample showed that a 7-profile solution fit the data best and this replicated to the testing sample. Profiles included a 'majority' profile (66.8%), high reward (4.3%) and low reward (4.0%) profiles, high inhibition (9.8%) and low inhibition (6.7%) profiles, and high affect (4.0%) and low affect (4.3%) profiles. The identified profiles differed significantly in sex (χ^2=25.28, p<.0001), race (χ^2=79.46, p<.0001), total family income (χ^2=122.17, p<.0001), cognitive performance (F=14.78, p<.0001), screen time (F=10.27, p<.0001), and several measures of impulsivity (p's<.00625). Relative to the majority profile, the smaller profiles were characterized by more males, higher proportions of individuals from lower-income households, poorer cognitive performance, more screen time, and heightened impulsivity.
Conclusions: These data support the presence of neurodevelopmental subgroups at the population level. They further indicate that these empirically derived, brain-based developmental profiles relate to individual differences in clinical features, even at a young age. We propose that these profiles will significantly differ in substance-use and other risk behaviors as assessed in future waves of the ABCD study.

Oral Communications I, Q&A

Big Data/Tech

3:30 p.m. - 4:30 p.m.

OPIOID TREATMENT MOBILE APPLICATION (OPTIMA) TO REDUCE RELAPSE AMONG ADULTS RECEIVING OUTPATIENT MAT: FACTORS ASSOCIATED WITH DAILY USE

G. Andrew James[*1], Ronald Thompson, Jr.[1], Blake Walden[1], Daphne Jackson[1], Nathan Jones[1], Laura Spell[1], Natalie Morris[1], Margaret Healy[1], Mary Bollinger[1], Michael Mancino[1], Clinton Kilts[1]*

[1]University of Arkansas for Medical Sciences

Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Treatment
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: We are conducting an ongoing experimental trial of OPTiMA (Opioid Treatment Mobile Application), a smartphone application (app) we developed as an adjunctive therapy to reduce relapse among adults receiving outpatient medication assisted treatment (MAT) for opioid use disorder (OUD). As OPTiMA is the first app-based intervention designed for adults receiving outpatient MAT for OUD, it is important to determine whether the targeted population will use it as directed and identify factors that attenuate such use. Thus, we provide preliminary findings on OPTiMA usage and factors related to its use.
Methods: Patients receiving MAT for OUD at the University of Arkansas for Medical Sciences (UAMS) were invited to participate in a three-month non-randomized experimental trial of OPTiMA. Participants used OPTiMA to record daily self-reports of craving intensity, withdrawal severity, stress, anger, and depression for the previous day. Participants also recorded illicit opioid, alcohol, and marijuana use. After completing daily self-reports, participants received personalized feedback to promote continued abstinence. Participants also received daily text reminders to use the app. Spearman's Rho analyses determined correlates of OPTiMA use.
Results: To date, we have enrolled seven participants (4 female, 3 male; 6 Caucasian, 1 African-American; median enrollment duration= 25 days, range = 14-49 days). Median daily participant use of OPTiMA was 59.18% of all possible days (range= 20.00–78.57 percent). Percentage of days OPTiMA was used was positively correlated with baseline stress (RHO = 0.8835, $p<0.0084$) and anger levels (RHO=0.9081, $p<0.0047$). Craving intensity, withdrawal severity, depression, and substance use were not significantly correlated with daily OPTiMA usage.
Conclusions: Despite small sample size, we found that participants used OPTiMA on more days than not and that higher stress and anger levels at baseline were associated with increased use. Study recruitment is ongoing.

PREDICTING COUNTIES AT-RISK OF A SYNTHETIC OPIOID OVERDOSE OUTBREAK: A STATISTICAL MODELING APPROACH

Charles Marks[1], Daniela Abramovitz[2], Christl A Donnelly[3], Daniel Ciccarone[4], Natasha Martin[2], Steffanie Strathdee[2], Annick Borquez[2]*

[1]San Diego State University, [2]University of California San Diego, [3]Imperial College London, [4]University of California San Francisco

Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Epidemiology
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Rather than a uniform increase in opioid-related mortality, the U.S. opioid crisis is the result of a series of geographically concentrated, drug-specific overdose outbreaks. This study aimed to evaluate the performance of a model built to predict counties at highest risk of synthetic opioid (i.e. fentanyl) overdose outbreaks in 2017, based on available data from 2012-2016, as a tool to predict future outbreaks.
Methods: Data on number of synthetic opioid overdose deaths by county (n=3143) were extracted from the CDC Wonder database and from the American Community Survey, Highway Safety Improvement Program, Esri and National Center for Health Statistics for potential predictors. We fit a time-dependent Cox regression model to 2012-2016 data that was then used to calculate predicted probabilities for outbreaks in 2017 in counties that had yet to experience one. Predictive performance was evaluated by comparing predictions to actual outcomes and calculating area under the (receiver operating characteristic) curve (AUC), accuracy, sensitivity, and specificity. Optimal cut-point was determined by maximizing sensitivity with a minimum specificity of 90%. In addition, we ran a 5-fold cross-validation on the training data to assess model overfitting.
Results: Our predictions had an AUC of 0.96, 90% accuracy, 92% sensitivity and 90% specificity, indicating strong overall performance. Of the 102 counties that newly experienced a synthetic opioid overdose outbreak in 2017, we correctly identified 94 (92%) at our optimal cut-point, including counties in Washington, Nevada, Minnesota, Iowa and Texas that were isolated from other counties experiencing such outbreaks. Cross-validation indicated the model was not overfit.
Conclusions: We show that, by leveraging observed data from 2012-2016, our model was able to accurately predict which counties would experience a synthetic opioid overdose outbreak in 2017. Having demonstrated model performance, next steps will entail predicting future overdose outbreaks, as such modeling forecasts can inform much needed preemptive responses.

SMART SYRINGE VENDING MACHINES – INTEGRATED SOLUTION FOR INTERVENTION DELIVERY AND RESEARCH DATA COLLECTION

David Otiashvili[*1], Irma Kirtadze[2], Tamar Mgebrishvili[1], Ada Beselia[1], Mzia Tabatadze[1], Nikoloz Otiashvili[1]*

[1]Addiction Research Center - Alternative Georgia, [2]Ilia State University

Abstract Detail: Human
Drug Category: Polydrug (i.e. Use of more than one drug combination)
Topic: Technology Issues
Abstract Category: Program Descriptions
Designation: M.D., Ph.D.

Abstract: Aim: Needle and syringe programs (NSP) are evidence-based intervention to prevent HIV infection among people who inject drugs (PWID). Syringe Vending Machines

(SVM) intend to supplement the standard NSP to reach hard to reach groups and to cover unserved geographical areas. The aim of the ongoing parent implementation trial is to evaluate the implementation process (and effectiveness) of SVM in Tbilisi, Georgia (country).
Conclusions: Six SVMs are operational in Tbilisi as of December 2019 and preliminary data suggests they are serving their purpose well. Our innovative solution integrates features for intervention delivery and research data collection. It can provide infrastructure for testing new research ideas and interventions (e.g. distribution HIV/HCV self-tests).

MACHINE LEARNING TO DESCRIBE POLYSUBSTANCE ABUSE IN CTN OPIOID TRIALS

Raymond Balise[*1], Layla Bouzoubaa[1], Edward Nunes[2], Sean Luo[3], Daniel Feaster[1]*

[1]University of Miami, [2]Columbia University and New York State Psychiatric Institute, [3]Columbia University

Abstract Detail: Human
Drug Category: Polydrug (i.e. Use of more than one drug combination)
Topic: Epidemiology
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: The Apriori machine learning algorithm is typically used to identify items frequently purchased together. It creates rules like "if you see peanut butter and jelly in a transaction, expect to see bread" ({PB, Jelly} => Bread). We used this method to detect recurring patterns of same-day drug use.
Methods: The substance abuse patterns for 2,456 individuals awaiting treatment for Opioid Use Disorder, as part of three National Drug Abuse Treatment Clinical Trials Network (CTN) trials CTN 27 (N = 1,236), CTN 30 (N = 665) and CTN 51 (N = 555), were analyzed using the Apriori pattern detection method. Apriori's performance is controlled by two hyperparameters; 1) support was set as 0.001 (i.e., limiting the analysis to drugs used on average at least twice in the 28 days) and 2) confidence was set at 0.5 (requiring 50% of days where one drug was used to feature the other drug). Results were assessed using confidence and lift (which standardizes confidence by the expected rate of co-occurrence).
Results: Subjects self-reported using drugs on 82% of the 28 days before treatment. On average, subjects used 1.4 drugs per day. After harmonizing drug names, 56,627 drugs events remained. A total of 88 patterns of two or more drugs were observed and 34 met the support and confidence criteria. Several strong rules (high on both confidence and lift) were noted including: Opium => Heroin and {Amphetamine, Methamphetamine} => Opioid. Other rules with high confidence included: Methamphetamine => Opioid; {Cocaine, Crack} => Opioid. Additional rules with large lift values included: {Cocaine, Heroin, Opioid} => THC; {Amphetamine, THC} => Heroin; Amphetamine => Heroin.
Conclusions: 88% of the most predictive patterns of co-occurrence of drug use included both stimulants and opioids. Better treatments for this pattern of substance abuse are needed.

Criminal justice

EXTENDED RELEASE INJECTABLE NALTREXONE BEFORE VS. AFTER RELEASE: A RANDOMIZED TRIAL OF OPIOID PRISONERS WITH OPIOID USE DISORDERS

George Woody[*1], *Sabrina Poole*[1], *Elmer Yu*[1], *John Carroll*[2], *Kevin Lynch*[1]

[1]*Perelman School of Medicine at the University of Pennsylvania,* [2]*Managing Partner Diagnostic Consultants*

Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Treatment
Abstract Category: Original Research
Designation: M.D.

Abstract: Aim: Determine if extended-release injectable naltrexone (XR-NTX) might be helpful to opioid addicted prisoners, particularly if given before release.
Methods: Consenting opioid-addicted prisoners in the Philadelphia County jail meeting study enrollment criteria were randomized to receive XR-NTX before release (BR) or in a community program after release (AR) along with counseling and three monthly followup doses. Followup assessments were attempted through month 6 after release.
Results: 402 prisoners expressed interest, 222 consented to participate, and 146 met enrollment criteria and were randomized. Uncertainty about sentencing and release dates resulted in a time lag between randomization and final disposition during which 60 were transferred, mandated to treatment, or otherwise became ineligible for study treatment. Due to high rates of missing urine drug screens and followup data on the remaining 86, we developed a phone-based questionnaire about opiate use and withdrawal to supplement other data and confirmed relapse or non-relapse for 63 of the 86. Relapse by month three was not significantly different for BR (39.5%) than AR (25%. Chisq [2] = 3.23, p = 0.20. BR patients received more XR-NTX than AR patients due to higher rates of receipt of the initial dose and rate of return for the second, but dropout was high and 21 were on XR-NTX at month 3 (12 BR, 9 AR), and 19 at month 4 (9 BR, 10 AR). No SAE's were associated with XR-NTX; all 16 overdoses, among them 4 deaths, were in patients that stopped or never took XR-NTX.
Conclusions: Prisoners were more likely to receive the first XR-NTX dose if it was offered BR but there was no significant difference in relapse by month 3, however the high proportion of missing data indicate this finding is inconclusive. The clustering of overdose reports in persons not on XR-NTX is consistent with the pharmacology of XR-NTX.

ASSESSING DOUBLE STIGMA AMONG PEOPLE MANDATED TO SUBSTANCE USE TREATMENT AFTER INCARCERATION: PILOT DATA ON A NEW MEASURE AND EVIDENCE OF CHANGE ACROSS TREATMENT

*Kelly Moore**[*1]

[1]*East Tennessee State University*

Abstract Detail: Human
Drug Category: Other, Any substance use disorder
Topic: Treatment

Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Justice-involved individuals with substance use disorders are subjected to negative stereotypes about crime and addiction (i.e., double stigma) in treatment settings. Qualitative studies highlight that this population expects to be judged (i.e., anticipated stigma) and feels ashamed of their identity (i.e., internalized stigma); however, quantitative research on these constructs is needed to understand a) unique vs. overlapping elements, and b) changes in stigma throughout participation in treatment.
Methods: Participants in an ongoing study were male and female probationers with felony convictions mandated to substance use treatment (n=21). Participants completed face-to-face interviews during week 1 and 6 of treatment. A measure of anticipated and internalized stigma associated with addiction (Stigma Mechanisms Scale; Smith et al., 2016) was adapted to assess stigma associated with criminal involvement, and both measures were administered at each timepoint.
Results: Anticipated and internalized stigma associated with addiction and crime (4 scales) demonstrated high internal consistency (Cronbach's $\alpha > .8$). Anticipated stigma associated with addiction and criminal involvement ($r=.93$, $p<.001$), and internalized stigma associated with addiction and criminal involvement ($r=.70$, $p<.001$) were highly correlated. Anticipated stigma associated with criminal involvement decreased from intake (M=30.4, SD=6.5) to 6 weeks (M=23.6, SD=8.4; Cohen's d=1.0), as did anticipated stigma associated with addiction (intake M=30.8, SD=7.1; 6 week M=26.3, SD=7.2; Cohen's d=0.6). Internalized stigma associated with criminal involvement decreased from intake (M=18.3, SD=6.2) to 6 weeks (M=15.2, SD=5.1; Cohen's d=0.5), as did internalized stigma associated with addiction (Intake M = 19.8, SD=4.7; 6 week M=16.2, SD=4.8; Cohen's d=0.8).
Conclusions: Stigma associated with criminal involvement and addiction significantly overlap and decrease similarly (with medium to large effect sizes) over the first 6 weeks of mandated substance use treatment. These preliminary findings demonstrate the malleable nature of double stigma, and future research should investigate treatment mechanisms that explain these reductions.

USE OF NON-PRESCRIBED BUPRENORPHINE DURING INCARCERATION: PERSPECTIVES OF FORMER INMATES

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Epidemiology
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: To characterize non-prescribed buprenorphine use (diversion) in jails/prisons.
Methods: A face-to-face structured interview was conducted with 300 adults with OUD/opioid misuse released from incarceration within the past 6 months in Maryland (where buprenorphine

treatment is not yet available for inmates) and New York (where buprenorphine treatment is available in jail/prison; n= 150 in each state). The interview queried use of non-prescribed buprenorphine and other drugs in jail/prison, perceived availability and cost, market dynamics, and motivations for using non-prescribed buprenorphine in the criminal justice system and the community.
Results: Participants were 82% male, 52% black, and 27% Hispanic ethnicity, with a mean (SD) age of 42 (10) years. Overall, 63% of participants reported using opioids during incarceration within the past 12 months, with 39% reporting non-prescribed buprenorphine use. Past 12-month substance use during incarceration differed by site for non-prescribed buprenorphine (47% MD vs. 31% NY; p<.01), heroin/illicit opioids (36% MD vs. 54% NY; p<.01), and methadone (5% MD vs. 15% NY; p<.01). Non-prescribed buprenorphine was perceived as widely available in the criminal justice system (81% reporting "very" or "somewhat" easy to get), but the average cost was ~10 times higher compared to the community. Participants were more likely to endorse non-therapeutic reasons for using non-prescribed buprenorphine during incarceration episodes (e.g., to get high), whereas therapeutic motives were more commonly ascribed to use in the community (e.g., to maintain abstinence from drugs).
Conclusions: Non-prescribed buprenorphine was perceived as widely available in criminal justice settings. Higher rates of non-prescribed buprenorphine use in MD compared to NY could be due to lack of availability of buprenorphine treatment in the MD criminal justice system, relative access to other drugs, or other factors. Different dynamics and demand characteristics may underlie use of non-prescribed buprenorphine in correctional settings compared to the community.

POST-TRAUMATIC STRESS DISORDER AMONG RURAL WOMEN WHO ENGAGE IN HIGH-RISK DRUG USE AND HAVE OVERDOSE EXPERIENCES

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Abstract Detail: Human
Drug Category: Other, General Substance Use
Topic: Behavior
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Understanding the relationship between overdose experiences and mental health following community re-entry from jail could help identify rural women in need of services. This secondary data analysis investigated overdose experiences before incarceration and symptoms of Post-Traumatic Stress Disorder (PTSD) among rural women transitioning from jail to the community.
Methods: High-risk drug-using women (n=400) were recruited in jails in rural Appalachia and completed a follow-up twelve-months post-release (n=352, 88%). Logistic regressions examined PTSD symptoms on the Global Appraisal of Individual Needs (GAIN) at follow-up as the dependent variable and independent variables of baseline overdose (OD) experience (i.e., no experience [n=127], witnessed an OD [n=98], experienced an OD [n=42], both witnessed and experienced an OD [n=85]), GAIN PTSD symptoms at baseline, and taking medication for a mental health condition at follow-up.

Results: Experiencing and witnessing an OD and taking a medication for a mental health condition were significantly associated with PTSD symptoms at follow-up ($X2(5)=28.3$, $p<0.001$). Women who both experienced and witnessed an OD before incarceration were almost three times more likely to experience PTSD symptoms at follow-up. In addition, odds of meeting PTSD criteria were two times higher for women who were taking medication for mental health at follow-up. PTSD symptoms at baseline was not significantly associated with symptoms at follow-up.
Conclusions: Rural women who have overdose experiences appear to be at increased risk of reporting PTSD symptoms as they transition to the community from jail. This highlights the ongoing need for mental health services, particularly for women who have experienced negative consequences of high-risk drug use. Future research should determine how providing mental health services through methods such as telehealth during incarceration and following community re-entry could help improve mental health among rural women who use drugs.

OPIOID USE DISORDER TREATMENT AND RELATION TO OVERDOSE DEATH AMONG A STATEWIDE POPULATION OF JUSTICE-INVOLVED ADULTS

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Treatment
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Justice-involved individuals have high rates of opioid-related morbidity and mortality and are an important target of policy initiatives to improve access to evidence-based treatment for opioid use disorder (OUD). This cohort study explored predictors of OUD treatment among justice-involved individuals in Maryland and the relationship between treatment with opioid agonists (OAT), and risk of fatal opioid overdose.
Methods: Records were obtained for persons with arrests, incarcerations, and community supervision related to property or drug crimes in Maryland in 2015-2016 (N=43,842) and were matched at the individual level to statewide databases for specialty substance use treatment, buprenorphine prescriptions, and opioid overdose deaths. Multivariate logistic regression was used to identify correlates of OAT and overdose risk among justice-involved adults who received OUD treatment.
Results: During 2015-2016, 17.5% justice-involved adults received treatment for OUD. Those treated for OUD were more likely to be female, white, of older age, and to have a misdemeanor drug charge arrest (vs. felony). Among those in treatment (N=6,982), 58% received OAT. Receiving treatment for alcohol, marijuana or cocaine use and being referred to treatment by a criminal justice source, reduced odds of receiving OAT. Black race and having received OAT during the study period were significantly associated with reduced odds of experiencing an opioid overdose death.
Conclusions: Almost one in five with criminal justice involvement received OUD treatment. While OAT reduces risk of overdose death among those receiving OUD treatment, many

justice-involved persons, especially those referred by criminal justice sources and those with co-occurring substance use conditions, do not receive OAT as part of their care. Efforts are needed to improve linkage to OAT among justice-involved persons receiving treatment in the community.

INTRODUCTION OF LONG-ACTING DEPOT BUPRENORPHINE IN PRISON - THE UNLOC-T STUDY

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Treatment
Abstract Category: Original Research
Designation: Prof., Dr., Med.

Abstract: Aim: This study was designed to assess the safety and feasibility of long acting injectable depot buprenorphine (BPN) for the treatment of adults with opioid use disorder in custodial settings in NSW, Australia. Study primary objectives were to (1) identify unexpected safety and tolerability considerations of depot BPN in adults in custody (2) assess diversion and other non-medical use of depot BPN and the impact on risk of violence and; (3) compare the time and cost associated with administration of depot BPN to standard care.
Methods: This prospective open-label case comparison trial compared long-acting depot BPN (CAM2038 weekly and monthly) to oral methadone across eight correctional centers in metropolitan and rural NSW, with a mix of adult (male and female) prisoner populations and security classifications. Data were collected on medical, dosing and correctional officer time for a cost consequences analysis comparing depot BPN to oral methadone and sublingual BPN.
Results: 129 participants were recruited across 8 correctional centers to depot BPN (n=67) or methadone (n=62), aged 36.4 (±8.4) years, 84% male, 39% Aboriginal/Torres Strait Islander, 44% with a history of overdose and 17% with a history of opioid agonist therapy (OAT) diversion in prison. Costs per-patient per-month for depot BPN, methadone and sublingual BPN were $44, $277 and $737 respectively. Data on drug safety (adverse events); drug use (baseline, 4 weeks, 16 weeks); opiate withdrawal; physical/mental health and quality of life; and treatment satisfaction will be presented.
Conclusions: In NSW, Australia, the current standard of care for opioid use disorder in prisons is daily orally or sublingually administered OAT, which is resource-intensive and associated with medication diversion, particularly of sublingual buprenorphine. While answering critical setting-specific safety and tolerability questions, this study will improve understanding of the

potential health economic impact and resource utilization with depot buprenorphine treatment in custodial settings compared to standard care.

ASSOCIATIONS BETWEEN RECENT INCARCERATION AND SUBSTANCE USE POST RELEASE AMONG A COHORT OF BLACK MEN WHO HAVE SEX WITH MEN AND BLACK TRANSGENDER WOMEN IN THE UNITED STATES: THE HPTN061 STUDY

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Abstract Detail: Human
Drug Category: Polydrug (i.e. Use of more than one drug combination)
Topic: Substance Use Disorder
Abstract Category: Original Research
Designation: M.S

Abstract: Aim: The disproportionate incarceration of black men who have sex with men and black transgender women (BMSM/BTW) is associated with many negative health outcomes after release. Substance use is associated with many negative outcomes including increased injection, sexual risk behavior, and overdose. Incarcerated BMSM/BTW may be more vulnerable to substance use. Our objective was to test associations between incarceration history and substance use post-release among BMSM/BTW.
Methods: We used data from the HIV Prevention Trials Network 061 (HPTN061) study (N=1155) to estimate associations between past 6-month incarceration and post-release binge drinking and illicit drug use among BMSM/BTW in six cities in the United States. Bivariate and multivariable models were constructed using inverse probability of treatment weighting (IPTW) to control for pre-incarceration substance use and 25 demographic and risk behavior confounders.
Results: At 12-month follow-up, BMSM/BTW reported different substance use prevalence ranging from 2% for heroin use to as high as 48% for marijuana use. Controlling for substance use at baseline, recent incarceration was associated with binge drinking (AOR: 1.47, 95% CI: 1.05, 2.04) and crack-cocaine use (AOR: 2.21, CI: 1.47, 3.33) six-months post-release. In fully adjusted analyses with IPTW, incarceration remained associated with crack cocaine use (AOR: 1.53, 95% CI: 1.03, 2.23) with similar, but non-significant findings for methamphetamine (AOR; 1.52 95% CI: 0.94, 2.45) six-months post-release.
Conclusions: The findings from this study highlight important associations between recent incarceration and post-release substance use, particularly for alcohol and stimulant use, which are often associated with sexual risk behaviors among sexual minority populations.
Further research should examine harm reduction programs aimed at reducing stimulant use among post-incarcerated individuals, with specific focus on BMSM/BTW. Integration with existing harm reduction and treatment programs for sexual minorities is needed, particularly in cities with high prevalence of stimulant use.

Epidemiology

REDUCTION IN WORLD HEALTH ORGANIZATION (WHO) DRINKING RISK LEVELS AND CARDIOVASCULAR DISEASE (CVD): 3-YEAR FOLLOW-UP RESULTS IN THE US GENERAL POPULATION

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Abstract Detail: Human
Drug Category: Alcohol
Topic: Epidemiology
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Non-abstinent drinking reductions could be useful clinical trial efficacy indicators if they offer clinical benefit and broaden interest in treatment for those uninterested in abstinence.
goals. Non-abstinent reductions in WHO risk drinking levels have recently been shown to lower the risk of alcohol dependence, depression/anxiety, drug use disorder and liver disease. This study examined the relationship between reductions in WHO risk drinking levels and subsequent risk for CVD.

Methods: In a US national survey (NESARC), 1,058 very-high-risk and high-risk drinkers participated in Wave 1 interviews (2001-2002) and Wave 2 follow-ups 3 years later (2004-2005). Self-reported CVD history included: arteriosclerosis, hypertension, angina, tachycardia, or myocardial infarction. We used logistic regression to estimate adjusted odds ratios (aOR) evaluating relationships between >2-level reductions in WHO risk drinking levels from Wave 1 to Wave 2 and the risk of Wave 2 CVD, controlling for baseline demographic variables and health characteristics. Tests of 3-way interaction were subsequently conducted for alcohol dependence and age group.
Results: Reductions of >2 WHO risk drinking levels were associated with significantly lower odds of CVD at 3-year follow-up in Wave 1 very-high-risk (aOR=0.58 [0.41-0.80]) and high-risk drinkers (aOR=0.81 [0.70-0.94]). Interaction terms showed this relationship varied by age. Notably, reductions of >2 WHO risk drinking levels were associated with significantly lower odds of CVD in Wave 1 very-high-risk drinkers initially >40 years old (aOR=0.42 [0.28-0.63]) and high-risk drinkers initially <40 years old (aOR=0.50 [0.37-0.69]).
Conclusions: These results provide evidence that non-abstinent reductions in WHO risk drinking levels are associated with reduced CVD risk among very-high-risk and high-risk drinkers in the US general population. This study adds to a growing body of evidence that non-abstinent reduction in high levels of drinking provide meaningful benefit across multiple clinical domains, including indicators of psychiatric status and health functioning.

TRENDS IN BUPRENORPHINE ABUSE, MISUSE, AND DIVERSION: RESULTS FROM THREE UNITED STATES NATIONAL DATA SOURCES

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Epidemiology
Abstract Category: Original Research
Designation: Sc.D.

Abstract: Aim: Buprenorphine is a safe and effective treatment for opioid use disorder (OUD), although there are concerns about its abuse, misuse, and diversion (AMD). This report examines trends in buprenorphine AMD using data from three US national data sources.
Methods: Trends of AMD for buprenorphine and other opioids were estimated using the following datasets. Diversion: 2010-2017 National Forensic Laboratory Information System (NFLIS) uses reports from drug cases submitted to and analyzed by federal, state, and local forensic laboratories; Abuse/Misuse: 2015-2017 National Survey on Drug Use and Health (NSDUH) – survey of the US non-institutionalized population; Abuse/Misuse: 2011-2017 Treatment Episode Dataset (TEDS) - national data system of annual admissions to substance abuse treatment facilities.
Results: For NFLIS, the number of drug reports for buprenorphine increased every year from 2010-2017, although the rate per dosage units dispensed was generally steady. In contrast, drug reports for oxycodone, hydrocodone, and methadone declined. For NSDUH, the prevalence of past-year misuse of buprenorphine in the US (2017 population: ~272.1 million) was 0.3% from 2015-2017, lower than more widely used opioids such as hydrocodone (2.3% in 2017) and oxycodone (1.4% in 2017), and similar to other opioids. Two thirds of those who misused buprenorphine met diagnostic criteria for OUD (68%). Prevalence of past-year buprenorphine misuse was 25% among those with OUD vs <0.1% for those without OUD. For TEDS, reports of buprenorphine as the primary substance problem have been increasing since 2011. Buprenorphine accounts for less than 1% of all opioid admissions.
Conclusions: Prevalence of buprenorphine abuse/misuse is relatively low in the general population and is concentrated among those with OUD, although it is rarely a primary drug problem among those entering treatment. Buprenorphine diversion has increased as utilization has increased. Greater understanding of the nature of buprenorphine AMD is necessary to inform policy and practice.

CHARACTERISTICS OF PRESCRIBERS OF OPIOID AGONIST TREATMENT USING ROUTINELY COLLECTED ADMINISTRATIVE DATA LOOKING AT RETENTION AND PROFILES OF BOTH PATIENTS AND THE PRESCRIBER IN NSW, AUSTRALIA

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Epidemiology
Abstract Category: Original Research
Designation: M.Sc.

Abstract: Aim: There has been a lot of research regarding people receiving opioid agonist treatment (OAT) such as methadone or buprenorphine, but very little on the prescribers of OAT. This paper aims to characterize the prescribers in terms of tenure, patient case load, and practice type. The retention of the prescriber was of primary interest, and secondary their patients, as a concern was raised regarding an aging prescriber base.
Methods: There were 2,194 prescribers from the administrative data for all people receiving OAT in New South Wales (NSW), Australia between 2001 and 2018. Descriptive statistics were used to summarize the acquisition and retention of prescribers annually.
Results: As of 2017 more prescribers were discontinuing prescribing OAT than new prescribers were starting. In 2018 approximately 75% of the OAT client base was under the care of 20% of the OAT prescribers (n=114), half of these (n=58) had been providing OAT for 17 years or longer. The highest attrition of prescribers is in the tenure group of less than 5 years, this group's attrition has been growing over the years, from 6% in 2002 to 21% in 2017.
Conclusions: Along with an aging prescriber base, steps will need to be taken to ensure prescribers are retained, and new prescribers are acquired to ensure OAT remains to be widely accessible to those in need.

PREVALENCE OF CANNABIS USE, DAILY CANNABIS USE AND CANNABIS USE DISORDER BY GENDER AND RACE/ETHNICITY AFTER ENACTMENT OF RECREATIONAL CANNABIS LAWS IN THE U.S FROM 2008-2017

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Abstract Detail: Human
Drug Category: Marijuana/Cannabinoids
Topic: Epidemiology
Abstract Category: Original Research
Designation: M.D.

Abstract: Aim: Little is known about potential changes in cannabis use outcomes by gender and race/ethnicity after the enactment of recreational cannabis laws (RCL).
Methods: Repeated cross-sectional survey data from the 2008-2017 National Survey on Drug Use and Health restricted use files (n=836,600; ages 12+). We examined changes in cannabis use outcomes—past-year and past-month cannabis use, past-year daily cannabis use, and past-year DSM-5 cannabis use disorder (CUD) among people reporting cannabis use—before and after RCL enactment by gender (men/women) and race/ethnicity (non-Latino White, non-Latino Black, Latino, and Other). We estimated adjusted prevalence differences for each cannabis use outcome comparing the period before and after RCL enactment by gender and race/ethnicity, controlling for historical trends and use over time.

Results: After RCL enactment, there were significant increases among men in past-year cannabis use (18.0%-19.8%, aPD:2.59, 95%CI:0.68,4.50]) but not on daily cannabis use (10.4%-12.6% (aPD:2.24[-0.13,3.67]), past-month cannabis use remained unchanged. Significant increases in cannabis use were observed among women, including past-year cannabis use (11.7%-16.2%, aPD:4.54[2.92,6.16]), past-year daily cannabis use (9.5%-13.7%, aPD:4.12[0.15,4.49]), and past-month cannabis use (6.2%-9.4%, aPD:3.20[1.97,4.42]). Among non-Latino Whites, past-year cannabis use increased significantly from 15.9% to 19.6% (aPD:3.75[1.99-5.49]) as did past-year daily cannabis use (13.0%-17.1%, aPD:4.13[0.75,7.52]) and past-month cannabis use (8.9% to 11.7%, aPD:2.81[1.42,4.20]). There were no prevalence changes among people of other race/ethnicities, among whom prevalences were all lower than among non-Latino Whites. There were no changes in past-year CUD among cannabis users by gender (range: 13.0%-17.6%) or race/ethnicity (range: 13.0% to 18.6%) following RCL enactment.
Conclusions: Overall, significant increases in cannabis use were observed in past-year use only for men, and in past-year use, past-year daily use and past month use for women and non-Latino Whites post-RML, CUD among cannabis users did not change post-RML. Findings call for more refined analyses on how RCL modifies cannabis consumption in different demographic subgroups.

EMERGING STIMULANT MORTALITY TRENDS BY ACTIVE INGREDIENT

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Abstract Detail: Human
Drug Category: Stimulants
Topic: Epidemiology
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Prescription stimulant mortality is under-studied in literature. Drug overdose deaths have continued to rise in the United States. Much attention has been given to opioids, but mortality rates increased for psychostimulants from 2015 to 2016. Previous studies provide a broad overview of mortality using ICD-10 codes to identify psychostimulant overdose, but do not provide substance specificity beyond identifying deaths involving cocaine. This study measures stimulant mortality by the molecule listed on the death certificates and examines the trends.
Methods: Record-level data from the 2010–2017 National Vital Statistics System Mortality files were linked to the Dug Mentions with Involvement (DMI) database, which contains a list of drug substances found on death certificates. Prescription stimulants investigated were amphetamine, lisdexamfetamine, dextroamphetamine, methylphenidate, atomoxetine, and modafinil. Non-prescription stimulants include cocaine, methamphetamine, 3,4-methylenedioxymethamphetamine, pseudoephedrine, and bath salts. Oxymorphone was included as a comparator.
Results: The stimulant mortality rate has increased from 2.9 in 2010 to 9.7 per 100,000 population- more than a three-fold increase. This amounts to 31,515 deaths, up from 9,022 deaths in 2017. The majority of those deaths are attributed to non-prescription stimulants (n= 30,461, 96.7%). Of notable increase, methamphetamine increased from 2,309 deaths in 2010

to 13,116 deaths in 2017 (5.7-fold increase). Mortality also increased for amphetamine (4.9-fold), methylphenidate (1.6-fold), and pseudoephedrine (2.6-fold). The peak of oxymorphone mortality was in 2016 with 1,139 deaths. Amphetamine had close to double that number of deaths in 2017 (n = 2,023), which is a 2.6-fold increase from 2010.
Conclusions: Psychostimulant mortality has risen substantially, and multiple molecules have contributed. Misclassification of amphetamine and other stimulants could be present. While there has been a large push to increase regulations on opioids, there is a need to monitor the deaths resulting from stimulant overdose and improve reporting accuracy for stimulants.

QUIT RATIOS FOR CIGARETTE SMOKING AMONG INDIVIDUALS WITH OPIOID USE AND OPIOID USE DISORDER IN THE UNITED STATES

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Epidemiology
Abstract Category: Original Research
Designation: M.P.H.,M.S.,Ph.D.

Abstract: Aim: The prevalence of cigarette smoking is 4-6 times higher among individuals who use opioids and/or have an opioid use disorder (OUD) compared to those who do not. Overall, smoking cessation has increased over time although it is unknown whether it has similarly increased for those with opioid use or OUD. The current study examined cigarette quit ratios from 2002-2017 among US individuals with and without opioid use or OUD.
Methods: Data came from the National Surveys on Drug Use and Health, a yearly cross-sectional survey of US civilians 12 years or older. Annual quit ratios (i.e., the proportion of former smokers among ever-smokers) were estimated from 2002-2017 overall and by sex. Linear regression tested time trends in quit ratios by opioid use/OUD.
Results: Past-month smoking prevalence was much higher for persons with, compared to without, OUD (73.6% versus 26.5%) or opioid use (64.8% versus 26.1%). In 2017, quit ratios for individuals with opioid use (18.5%) or OUD (16.8%) were less than half the quit ratios of those without opioid use or OUD (49.4% and 49.1%, respectively). After adjusting for demographics and other drug use/drug use disorders, the quit ratio did not change among individuals with opioid use/OUD in contrast to a non-linear increase in quit ratios for those with OUD and those with no opioid use/OUD. For all years, compared to males, females with no opioid use/OUD were less likely to be former smokers. There were no differences by sex for individuals with opioid use/OUD.
Conclusions: While quit ratios increased from 2002-2017 for persons without opioid use or OUD, cigarette smoking quit ratios remain dramatically lower among those who use opioids or have OUD compared to those who do not. Public health and clinical attention are needed to increase cessation and reduce harmful cigarette smoking consequences for individuals with opioid use and OUD.

SUBSTANCE USE PATTERNS AMONG PEOPLE WITH DISABILITIES

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Abstract Detail: Human
Drug Category: Other, Marijuana, prescription opioid, other drugs, tobacco
Topic: Epidemiology
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Little is known about substance use patterns among people with disabilities, as existing research has relied on small and/or clinical samples of people with specific disabling conditions. Using a nationally representative household survey, we examined whether substance use was more common among people with disabilities.
Methods: Data are from the 2019-2020 National Alcohol Survey, a telephone- and web-based study of US adults. Logistic regression analyses first adjusted for key demographics, then accounted for chronic pain and mental distress.
Results: Preliminary unweighted findings from 1,459 respondents (average age 47; 38% male; 20% Hispanic/Latino, 22% Black/African American, 14% other race/ethnicity) show 19% reported a disability indicator (sensory or mobility impairment, receiving Medicare while under age 65, no exercise due to disability, and/or no employment due to disability), 34% reported chronic pain and 5% reported distress. Compared to people without a disability, people with a disability were significantly more likely to be daily smokers, misuse prescription drugs and use non-prescription drugs other than marijuana; they were not more likely to use marijuana or have a medical marijuana recommendation. The proportions with chronic pain and distress each were significantly greater among people with a disability, and pain and distress were significantly associated with daily smoking and prescription drug misuse, but not marijuana use. Further analyses will extend the sample, use weighted data, and examine chronic pain and distress as mediators.
Conclusions: Smoking and some recreational drug use are more common among people with disabilities, although marijuana use (recreational or medical) is not. Prescription opioid misuse is increased, which might reflect greater opportunity given higher prescription opioid rates and chronic pain among people with disabilities. These findings highlight the need to provide accommodations and accessible substance use treatment facilities to ensure that the needs of people with disabilities are met.

EPIDEMIOLOGY OF BENZODIAZEPINE MISUSE AMONG OLDER ADULTS IN THE UNITED STATES

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Abstract Detail: Human
Drug Category: Other, Benzodiazepines

Topic: Epidemiology
Abstract Category: Original Research
Designation: M.Sc.

Abstract: Aim: Benzodiazepine (BZD) prescription rates remain high among older adults. Co-use of BZD and other drugs increase the risk of cognitive decline, falls, motor vehicle accidents, and accidental overdose. This study aims to estimate the past-year prevalence and correlates of tranquilizer-type BZD use and misuse among older adults in the United States. We hypothesized that BZD misuse would be more strongly associated with more severe patterns of alcohol, tobacco, cannabis and prescription pain reliever use.
Methods: Data from 35,229 older adults (50+ years old) surveyed in the 2015-2018 National Study on Drug Use and Health (NSDUH) were analyzed. Descriptive and multivariable logistic regression models were conducted to estimate the prevalence of BZD use and misuse, and to identify associated correlates. NSDUH analysis weights were applied to accommodate for the sampling design.
Results: Nearly 1 in 8 older adults reported past-year BZD use, with 1 in 12 users reporting misuse. Compared to non-users, individuals with a past year diagnosis of cannabis use disorder (aOR = 5.4, 95% CI = 2.2, 13.1), alcohol use disorder (aOR = 4.6, 95% CI = 2.7, 8.1), or prescription pain relievers use disorder (aOR = 9.8, 95% CI = 5.8, 16.8) were more likely to misuse BZD. Among those who misused BZD in the past-year, 86.4% indicated it was for medical reasons, 6.8% recreational, and 6.8% unknown.
Conclusions: This study contributes to the literature by providing a more detailed assessment of BZD use and misuse and co-use of other drugs among older adults in the US. Our results suggest that BZD misuse is highly prevalent among older adults with cannabis, alcohol, and pain reliever use disorders. As BZD prescriptions continue to grow, further research should investigate how specific reasons for BZD misuse contribute to modify the course and patterns of use of other drugs.

Extended Outcomes

MEDICATION STATUS, OPIOID ABSTINENCE, AND RELAPSE FOLLOWING THE X:BOT TRIAL

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Treatment
Abstract Category: Original Research
Designation: M.D.,M.P.H.

Abstract: Aim: To describe medication status, opioid abstinence, and relapse following the X:BOT head-to-head comparative effectiveness trial of buprenorphine-naloxone (BUP-NX) and extended-release naltrexone (XR-NTX).
Methods: This report includes data from the National Drug Abuse Treatment Clinical Trials Network CTN-0051 trial (X:BOT) which randomized 570 participants recruited from eight community-based detoxification programs to BUP-NX (n=287) or XR-NTX (n=283) for up to 24 weeks of outpatient treatment. Upon conclusion of the trial, participants were managed by the same treatment programs or referred elsewhere in the community. Intensive efforts were made to include all participants including dropouts and induction failures at week 36 follow-up.
Results: 430 individuals were assessed at week 36 (225 from the BUP-NX treatment arm and 205 from the XR-NTX treatment arm). Of these 430 individuals at week 36, 52% were on medications for opioid use disorder (MOUD) and 48% were not. Thirty-three percent of those on MOUD and 33% of those off MOUD were abstinent from non-study opioids. Twenty-three percent of those on BUP-NX, and 54% of those on XR-NTX were abstinent. Sixteen percent of those on MOUD and 39% of those off MOUD met study criteria for relapse. Thirteen percent of those on BUP-NX and 15% of those on XR-NTX met study criteria for relapse.
Conclusions: In naturalistic follow-up in the community, about half of the individuals evaluated three months following the 24-week trial were on MOUD and about half were not. Those on MOUD were less likely to have met study relapse criteria. There were no differences in abstinence rates between those on, and those not on MOUD. Across study arms, those assigned to XR-NTX were more likely than those assigned to BUP-NX to be abstinent. Both groups were similarly likely to have met study criteria for relapse.

OVERDOSE AND HOSPITALIZATION AFTER TREATMENT WITH MEDICATION OR RESIDENTIAL TREATMENT FOR OPIOID USE DISORDERS

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Treatment
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: To compare the effectiveness of inpatient detoxification and/or residential treatment (inpatient) for opioid use disorder (OUD) to outpatient medication treatment for opioid use disorder (MOUD) by evaluating opioid-related overdose and all-cause hospitalization rates after each treatment modality using national medical claims data. We hypothesized that after accounting for selection bias in treatment choice, MOUD would result in better health outcomes than inpatient.
Methods: We used data from MarketScan, a large commercial claims database, to construct a cohort of individuals diagnosed with OUD and initiating either inpatient or MOUD treatment from 2010 to 2017. We used propensity score matching to create a 1-1 matched sample of initial MOUD and inpatient treatment episodes where the matching score was a function of

age, sex, region of residence, receipt of rescue naloxone, occurrence of an overdose prior to treatment, and presence of concurrently diagnosed substance use disorders. We employed a Cox proportional hazards model to predict time to first overdose and hospitalization following treatment initiation for the matched samples.
Results: Our cohort included 78,040 individuals, split equally between those initiating inpatient treatment and MOUD treatment. In the inpatient sample the incident rate of overdose and hospitalization was 4.5 and 78.7 events per 100-person years, respectively, while for the MOUD sample rates were 2.4 and 44.4 overdoses and hospitalizations per 100-person years. Patients in the inpatient sample progressed to hospitalization and overdose faster with a hazard ratio of 2.1 (95% CI 2.0-2.3) and 1.9 (95% CI 1.8-1.9), respectively compared patients initiating MOUD. We were unable to detect a difference in outcomes between short term (detoxification) and long term (residential) inpatient episodes.
Conclusions: Among commercially insured patients, treating patients with MOUDs is associated with a lower incidence of overdose and subsequent hospitalization than inpatient treatment.

CHARACTERIZING PATIENT OUTCOMES AFTER TREATMENT: RESULTS OF THE RECOVER 24-MONTH OBSERVATIONAL STUDY

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Substance Use Disorder
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: While the opioid epidemic continues to be in the public spotlight, treatment and associated outcomes have garnered less attention. This analysis aims to characterize the 24-month outcomes of treatment-seeking opioid use disorder patients after participation in Phase 3 clinical trials for buprenorphine extended release (BUP-XR).
Methods: The RECOVER (Remission from Chronic Opioid Use: Studying Environmental and Socioeconomic Factors on Recovery) observational study (NCT03604861) followed participants after exiting BUP-XR trials (NCT02357901, NCT02510014) for up to 24 months. Outcomes included treatment, substance use, psychosocial, and economic outcomes.
Results: Of the 533 participants enrolled in RECOVER, 396(74.3%) completed the 24-month assessment. Over the entire 24-month period, 342(64.1%) reported receiving further treatment for substance use disorder, of which 142(26.6%) received BUP-XR through an ongoing study (NCT02896296). Of 302 participants who completed the Treatment Effectiveness Assessment measure at 24 months, mean (SD; median) scores measuring the degree of change since initiating the BUP-XR trial (range 1 [no change] - 10 [much better]) were 7.2(3.3;8.0) for substance use, 7.0(2.8;7.0) for health, 7.4(2.7;8.0) for lifestyle, and 6.9(3.1;7.0) for community. Key themes in open-ended responses included no longer feeling sick, having a job/money, being clean/sober, improving family relationships, and having positive impact on others. These results are supported by study outcomes, including 71.7% reporting past week abstinence from opioids at the 24-month assessment with 44.7% reporting abstinence for the entire 24 month

period; health measured by the SF-12 physical and mental component summary scores approaching US-based norms of 50 (physical= mean 47.0[SD 9.9;median 49.7]; mental=46.9[12.3;48.6); 46.7% employment at 24 months; and 97.7% without felony and 92.4% without misdemeanor arrests based on public records during the RECOVER study period.
Conclusions: Opioid use disorder is a chronic disorder and its treatment is complex and multifaceted. This cohort demonstrates life changes for the better, extending 24 months and more beyond initial treatment.

Fentanyl

TAKE HOME DRUG CHECKING AS A NOVEL HARM REDUCTION STRATEGY IN BRITISH COLUMBIA, CANADA

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Other
Abstract Category: Original Research
Designation: M.D.

Abstract: Aim: Drug checking is a harm reduction strategy used to identify components of illicitly obtained drugs, including potential adulterants, and prevent overdose. This study evaluated distribution of take-home fentanyl test strips to people who use drugs (PWUD) in British Columbia, Canada. The primary aim was to determine the effectiveness of take-home drug checking in terms of detecting fentanyl in opioid samples with secondary aims being to assess the feasibility and acceptability of this strategy to PWUD.
Methods: Take home fentanyl test strip kits were distributed at 10 sites providing on-site drug checking services. Results from take home and on-site drug checking were compared over a three-month period. A survey was used to collect information about acceptability and behaviour change. For the primary outcome, this was a binary outcome equivalence trial with a pre-defined equivalence limit of +/-5%. This study was not restricted by gender.
Results: A total of 1680 take home results were obtained from 218 participants; 73% were for drugs identified as opioids. The difference between fentanyl positivity of opioids tested using take home drug checking and on-site drug checking was 0.81% (95% CI -2.27% to 3.89%). These results were not affected by gender, First Nations ethnicity, or previous experience with test strips. Fentanyl positivity of stimulants (cocaine, crystal methamphetamine) tested using take home drug checking was higher than drugs tested using on-site drug checking (24.86% vs. 3.17%). 27% of individuals reported behaviour change that was considered safer/positive associated with a fentanyl positive result. Greater than 95% of participants stated they would use fentanyl test strips again.

Conclusions: Take home drug checking of opioids was equivalent to on-site drug checking. Fentanyl positivity in stimulants may not be equivalent, suggesting a need for further education and evaluation. This harm reduction strategy is feasible and acceptable to PWUD.

FENTANYL-TARGETED VACCINE ATTENUATES FENTANYL-VERSUS-FOOD CHOICE IN RHESUS MONKEYS

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Abstract Detail: Animal Study
Drug Category: Opiates/Opioids
Topic: Treatment
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Opioid-targeted vaccines are under consideration as candidate Opioid Use Disorder medications. A recent study reported a fentanyl-targeted vaccine produced a robust and long-lasting attenuation of the choice of fentanyl over a food alternative in rats. In the current study, an optimized fentanyl-targeted vaccine was evaluated in rhesus monkeys to determine whether vaccine effects translated to a species with greater phylogenetic similarity to humans.
Methods: Adult male (2) and female (3) rhesus monkeys were trained to respond under a concurrent schedule of food (1g pellets, fixed-ratio 100 schedule) and intravenous fentanyl (0, 0.032-1 µg/kg/injection, fixed-ratio 10 schedule) reinforcement during daily 2h sessions. Fentanyl dose-effect functions were determined daily during 7-day buprenorphine treatments (0.0032-0.032 mg/kg/h IV; n=4-5) as well as during a 20+ week evaluation of the effects of a conjugate fentanyl-CRM vaccine (n=3; vaccinations at week 0, 3, 8, 15).

Results: Buprenorphine produced a significant decrease in fentanyl choices and a reciprocal increase in food choice in all monkeys (interaction: $F_{1.9,5.07}=6.76$, $p=0.038$). Vaccination eliminated choice of fentanyl and increased food choice by week 8 in one monkey and by week 15 in a second monkey. A more transient and less robust (~3-fold shift) vaccine effect was observed in a third monkey. Vaccine studies are ongoing in the fourth and fifth monkeys.
Conclusions: These results translate fentanyl vaccine effectiveness from rats to rhesus monkeys to decrease fentanyl vs. food choice, albeit with more individual differences observed in monkeys. Moreover, these results support the potential of opioid-targeted vaccines as candidate Opioid Use Disorder medications. Further details regarding the effectiveness, time course, antibody titer, and affinity of this vaccine will emerge as additional timepoints and subjects are evaluated.

SELF-REPORTED MEDICAL AND NON-MEDICAL PRESCRIPTION FENTANYL USE IN A HOUSEHOLD SAMPLE OF US ADULTS IN 2015-2017: ASSOCIATIONS WITH OTHER SUBSTANCE USE

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Abstract Detail: Human
Drug Category: Polydrug (i.e. Use of more than one drug combination)
Topic: Epidemiology
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: While illegally produced fentanyl is strongly associated with overdose risk and mortality, fentanyl can also be prescribed for medical reasons (e.g., post-surgical pain). However, little is known about the characteristics of adults who self-report medical and non-medical prescription fentanyl use, or its association with other substance use.
Methods: Data included adult men and women from the 2015-2017 National Survey on Drug Use and Health (N=128,740). Adults self-reported past-year pain reliever use, including prescription fentanyl, and indicated whether the fentanyl was used non-medically (i.e., "in a way a doctor did not direct"). We estimated unweighted prevalence of any past-year fentanyl use, and calculated the proportion reporting non-medical use. Logistic regression estimated odds of non-medical vs. medical fentanyl use adjusting for sociodemographic and substance use characteristics.
Results: In this community-based household sample of adults, 0.8% (n=1,068) reported any prescription fentanyl use. Among adults reporting any past-year use, 81.2% (n=857) reported medical use only, while 19.8% (n=211) reported non-medical prescription fentanyl use. Among adults reporting non-medical fentanyl use, 97.6% also reported other prescription opioid use, 49.8% heroin, 64.9% prescription sedatives/tranquilizers, 45.0% cocaine, and 73.0% prescription stimulant use. About half (48.3%) of adults reporting non-medical fentanyl use also reported past-month binge drinking, and 37.9% reported daily cigarette use. Compared to medical prescription fentanyl use only, any non-medical prescription fentanyl use was associated with past-year heroin (aOR=5.5, 95%CI=3.3-9.1), past-year prescription sedative/tranquilizer use (aOR=4.7, 95% CI=3.1-7.2), and daily cigarette use (aOR=1.8, 95% CI=1.3-2.6).
Conclusions: One in five adults who used prescription fentanyl did so in a way other than directed by a doctor. Polysubstance use was high among people reporting non-medical prescription fentanyl use, particularly heroin and sedative/tranquilizer use, which are associated with overdose risk. Additional services may be needed for people prescribed fentanyl in order to prevent potential fentanyl-related harms, particularly among those reporting non-medical use.

VACCINES TO COUNTERACT ILLICIT USE AND PREVENT FATAL OVERDOSE OF FENTANYL AND ITS ANALOGS

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Abstract Detail: Animal Study
Drug Category: Opiates/Opioids
Topic: Treatment
Abstract Category: Original Research
Designation: M.S.

Abstract: Aim: North America and Europe have seen dramatic increases in fatal overdoses due to the widespread illicit use of drug mixtures containing fentanyl and fentanyl-like analogs. To address this public health treat, our team is currently developing vaccines to reduce and prevent toxicity from deliberate and accidental exposure to fentanyl and its derivatives.
Methods: This study describes the pre-clinical development of vaccine formulations containing a series of fentanyl-based haptens conjugated to GMP-grade carrier proteins. All haptens and conjugates were characterized for their biophysical properties by mass spectrometry and other standard analytical methods, and then tested in vivo. Mice and rats were immunized i.m. (n=6/group), and then challenged with single or multiple s.c. doses of fentanyl and its analogs. Before and after drug challenges, all subjects were tested for antinociception on a hotplate and for respiratory depression and bradycardia by means of an oximeter. Antibodies were analyzed by ELISA to determine titers and affinity for fentanyl, its analogs, and off-target opioids (e.g., naloxone). Finally, the lead vaccine formulation was tested in a fentanyl intravenous self-administration (FSA) rat model (n=6/group). All experiments included mice and rats immunized with unconjugated carrier proteins as control. Mean titers, nociceptive latency, oxygen saturation, and heart rate were compared across groups and/or over time by one- or two-way ANOVA paired to post-hoc tests as statistically appropriate.
Results: The most promising vaccine formulations were effective in blocking fentanyl-induced antinociception, respiratory depression, and bradycardia in both mice and rats. Polyclonal antibodies showed high affinity for fentanyl but also cross reactivity to its analogs. Vaccination was effective in reducing ongoing FSA in rats. Furthermore, immunized rats did not increase fentanyl intake to overcome vaccine efficacy during the FSA protocol.
Conclusions: These pre-clinical data support translation of vaccines as a strategy to counteract toxicity and prevent fatal overdoses from fentanyl and its analogs.

Health Disparities

RANDOMIZED CONTROLLED TRIAL OF A POSITIVE AFFECT INTERVENTION TO REDUCE HIV VIRAL LOAD AMONG SEXUAL MINORITY MEN WHO USE METHAMPHETAMINE

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Abstract Detail: Human
Drug Category: Stimulants
Topic: HIV/Immune
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: This randomized controlled trial (RCT), examined whether a positive affect intervention to sensitize individuals to natural sources of reward could boost the effectiveness of contingency management (CM) for stimulant abstinence.
Methods: From 2013-2017, 110 sexual minority men living with HIV who had biologically confirmed, recent methamphetamine use were enrolled. Participants were randomized to: 1) a five session, individually delivered positive affect intervention (n = 55) – Affect Regulation Treatment to Enhance Methamphetamine Intervention Success (ARTEMIS); or 2) an attention-matched control condition (n = 55). ARTEMIS and attention-control sessions were delivered over a three-month period where all participants received thrice-weekly CM for stimulant abstinence.
Results: The majority of participants were racial/ethnic minorities (57%), middle-aged (mean = 43.2 years; SD = 8.9), and 14% had an unsuppressed viral load at baseline. Men in the ARTEMIS intervention displayed significantly lower log10 HIV viral load at 6 (Cohen's d = 0.89), 12 (Cohen's d = 0.43), and 15 (Cohen's d = 0.50) months compared to attention-control participants. Men in the ARTEMIS intervention also had significantly lower risk of at least one unsuppressed HIV RNA over 15 months (Risk Ratio [RR] = 0.33; 95% CI = 0.15 – 0.69; $p < 0.001$). Men in the ARTEMIS intervention reported concurrent increases positive affect and decreases in the frequency of stimulant use at 6 and 12 months. Although ARTEMIS intervention participants had lower risk of providing one or more urine samples that were reactive for stimulants over the 15-month follow-up period, this did not reach statistical significance (RR = 0.80; 95% CI = 0.63 – 1.02; p = 0.056).
Conclusions: In this RCT with sexual minority men who use methamphetamine, delivering a positive affect intervention with CM for stimulant abstinence achieved durable virologic suppression that were paralleled by increases in positive affect and decreases in stimulant use.

POLYSUBSTANCE PATTERNS IN SEXUAL MINORITY MEN LIVING WITH HIV WHO USE METHAMPHETAMINE

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Abstract Detail: Human
Drug Category: Stimulants
Topic: HIV/Immune
Abstract Category: Original Research
Designation: M.P.H.

Abstract: Aim: This study examined the associations of demographics, structural factors, and sexual minority stress with distinct typologies of polysubstance use in sexual minority men living with HIV who use methamphetamine.
Methods: A total of 162 sexual minority men living with HIV who reported methamphetamine use in the past 3 months were recruited in San Francisco. A latent class analysis (LCA) was conducted to identify typologies of polysubstance use based on any self-reported use of 11 substances in the past 30 days. Race/ethnicity, homelessness in the last year, and sexual minority stress assessed using Cultural Assessment of Risk for Suicide (CARS) were examined as correlates of typologies of polysubstance use with a 3-step procedure of categorical latent variable logistic regression.

Results: Utilizing LCA and model fit statistics, four classes of polysubstance use were identified: 1) high polysubstance use (n = 4), 2) crack-cocaine and methamphetamine co-use (n = 83), 3) methamphetamine use only (n = 36), and 4) ChemSex – gamma-hydroxybutyrate (GHB), and methamphetamine use, and erectile dysfunction medication (n = 39). Compared to methamphetamine use only, the high polysubstance group had significantly higher odds of reporting homelessness, non-Hispanic ethnicity, and detectable viral loads (OR=-21.6, p <0.01; OR=26.2; p <0.01; OR=17.6, p<0.01, respectively). The crack-cocaine and methamphetamine co-use group had lower overall CARS scores and higher odds of detectable viral loads (OR= 0.293, p=0.04; OR=9.9,p<0.01, respectively), and the ChemSex group had significant differences in race and ethnicity (OR = -0.91, p <0.01; OR = 2.57, p=.023, respectively).
Conclusions: Findings underscore that polysubstance use typologies among sexual minority men living with HIV who use methamphetamine vary by race/ethnicity, housing status, and sexual minority stress. This underscores the need for tailored intervention approaches to address the unique contexts and consequences of distinct polysubstance use typologies in sexual minority men living with HIV who use methamphetamine.

METHAMPHETAMINE INJECTION: ASSOCIATIONS WITH MICROBIAL TRANSLOCATION, IMMUNE ACTIVATION, AND INFLAMMATION IN TREATED HIV INFECTION

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Abstract Detail: Human
Drug Category: Stimulants
Topic: HIV/Immune
Abstract Category: Original Research
Designation: M.S.

Abstract: Aim: People who use stimulants such as methamphetamine display alterations in pathophysiologic processes linked to faster clinical HIV progression. This study explores whether methamphetamine-associated immune dysregulation is more pronounced among those who engage in injection drug use (Meth IDU).
Methods: This cross-sectional study enrolled sexual minority men living with HIV with an undetectable viral load (< 40 copies/mL) and biologically confirmed, recent methamphetamine use. We examined if plasma biomarkers of microbial translocation, immune activation, and inflammation were elevated among Meth IDU relative to methamphetamine users who did not report IDU. Multiple linear regression models adjusted for age, antiretroviral therapy regimen, CD4+ T-cell count, and reactive urine toxicology results (Tox+) for stimulants.
Results: Eighty-six men aged 23 to 59 years old (mean age=43.7 years, SD=9.6 years) met inclusion criteria. They had a median CD4+ T-cell count of 645 cells/mm3. Meth IDU participants were significantly more likely to be homeless and Tox+ for stimulants. Even after adjusting for whether participants were Tox+ for stimulants, those reporting Meth IDU displayed elevated plasma levels of lipopolysaccharide binding protein (p<.001), soluble CD163 (p<.05), interleukin-6 (p<.01), and soluble tumor necrosis factor alpha receptor I

(p<.01). Although Meth IDU participants displayed elevated tumor necrosis factor alpha receptor II, these differences were not significant in adjusted analyses. Finally, there were no significant differences in soluble CD14 as a function of Meth IDU.
Conclusions: Even among methamphetamine users with treated HIV infection, those who engage in Meth IDU display exacerbations in key pathophysiologic processes linked with faster clinical HIV progression. Our findings highlight the importance of screening for Meth IDU, discussing safer injection practices, and providing linkages to needle exchanges. Even those who are not ready, willing, or able to abstain from methamphetamine use could derive important health benefits from avoiding Meth IDU.

OPPORTUNITIES AND CHALLENGES TO PILOTING A COMMUNITY-BASED DRUG-CHECKING INTERVENTION FOR YOUNG SEXUAL AND GENDER MINORITY MEN IN VANCOUVER, CANADA: A QUALITATIVE STUDY

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Abstract Detail: Human
Drug Category: Other, Drug Checking
Topic: Technology Issues
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Despite British Columbia's scale-up of harm reduction services, Vancouver faces a dramatic increase in fatal overdose rates due to an increasingly contaminated illicit drug supply. Illicit drug use among young sexual and gender minority men (YSGM) is higher than their heterosexual's counterparts. Therefore, a pilot community-based drug-checking intervention (DCI) for YSGM was implemented in Vancouver. This study aims to evaluate YSGM and key stakeholders' opinions about this pilot DCI.
Methods: This community-based DCI for YSGM occurred from July 2018 to March 2019 and provided access to fentanyl test strips, a Fourier-transform infrared spectrometer, and harm reduction materials (e.g., naloxone training). We conducted in-depth interviews with 50 YSGM ages 15-30 to assess their willingness to use drug-checking services, and with seven stakeholders (e.g., decision-makers, technicians) about their experiences designing and implementing the pilot intervention.
Results: YSGM participants expressed three primary themes: 1) an overall low levels of awareness about drug checking that was often shaped through previous exposure to DCIs (e.g., through music festivals); 2) a high level of acceptability of, and willingness to use, drug-checking in community-based settings; and 3) salient barriers DCI access including fear of criminalization, confidentiality and privacy.
Stakeholders emphasized three key factors: 1) models of DCIs offered in safe consumption sites must be adapted to address YSGM's unique needs and contexts of substance use; 2) future DCIs should include peer-based approaches to remain culturally responsive to the needs of YSGM; and 3) community-based DCIs should be adapted into mobile drug-checking services to better access hard-to-reach YSGM.
Conclusions: Our findings support the feasibility of implementing DCIs for YSGM as a means to improve access to information about substance use and to reduce potential harms, including

overdose. The involvement of community-based organizations in developing DCIs is needed to provide tailored services that address the specific needs of YSGM who use substances.

HEALTH DISPARITIES IN ACCESS TO HEALTH CARE, HIV INFECTION, SUBSTANCE ABUSE, AND MENTAL HEALTH AMONG LATINO MEN WHO HAVE SEX WITH MEN IN A U.S.- MEXICO BORDER CITY

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Abstract Detail: Human
Drug Category: Marijuana/Cannabinoids
Topic: Ethnic Differences
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Latino Men who have sex with men (MSM) living in the U.S. experience health disparities in terms of access to healthcare, HIV infection, substance use/abuse, and mental health. Little attention has been paid to Latino MSM living along the U.S.-Mexico border region. AIM: Therefore, the aim of this study was to describe health disparities in access to care, HIV infection, substance use/abuse, and mental health among a sample of Latino MSM residing in a U.S.-Mexico border city.
Methods: A cross-sectional study among 150 community-dwelling Latino MSM in a U.S.-Mexico border city. Baseline demographic characteristics, along with measures for healthcare access, HIV care, mental health, and substance use were collected. Descriptive statistics for all measures are reported.
Results: Median age of participants was 26 years and the majority of participants identified as a sexual minority (97.3%) and born in the U.S. (85.2%). Almost half of the participants did not have health insurance (51.0%). Among those tested (89.3%), 12.2% reported receiving a positive HIV antibody test result. Among those living with HIV infection (n=18), 16 were receiving medical care for HIV infection and had been living with HIV infection for a median of 30 months. Nearly half of the participants reported suicidal ideation (48.9%) and 17.4% reported a suicide attempt during the lifetime. Ten percent of the sample were receiving mental healthcare services. Substances most commonly used were alcohol (77.3%), cigarettes/tobacco (43.4%), and marijuana (32.4%).
Conclusions: Healthcare clinicians who provide care for Latino MSM need to be aware of the number of health disparities and intersecting co-morbidities experienced by this sub-population and the impact on overall health. Research studies are needed to begin work on a culturally appropriate intervention that could assist Latino MSM in managing these multiple health disparities and decreasing health risks.

HEALTH DIFFERENCES IN A NATIONALLY REPRESENTATIVE SAMPLE OF SEXUAL MINORITIES AND MEDICAL CANNABIS USERS

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Abstract Detail: Human
Drug Category: Marijuana/Cannabinoids
Topic: Alternative Medicine
Abstract Category: Original Research
Designation: APRN,NP,Ph.D.

Abstract: Aim: The aim of this study was to compare health status in heterosexuals and sexual minorities who are medical cannabis (MC) users and non-users.
Methods: Data come from the 2012-2013 NESARC-III, a nationally representative survey of the civilian non-institutionalized population of US adults aged 18 years and older (N=36,309). We examined the association of lifetime MC use (yes/no) with sexual identity (1. heterosexual, 2. gay or lesbian, 3. bisexual, or 4. not sure). Multiple logistic regression assessed the associations among MC use, sexual identity, physical illness, mental illness, and general health, as well as lifetime cannabis use disorder (CUD).
Results: Sexual minorities were more likely to report a physical illness (aOR=1.57, 95% CI=1.33-1.84, p<.001), and 2.6 more likely to report a mental illness (aOR=2.65, 95% CI=2.27-3.09, p<.001). Sexual minorities had higher odds of using MC (4.4% v 1.3%, aOR =3.05, 95% CI=2.18-4.25, p < .001) when compared with heterosexuals. Sexual minorities and heterosexuals who used MC reported similar physical (aOR=.73, 95% CI=.33-1.59, p=.421) and mental health (aOR=1.07, 95% CI=.54-2.1, p=.843). However, sexual minorities who have not used MC were more likely to report physical illness (aOR=1.57, 95% CI=1.33-1.84, p<.001) and mental illness (aOR 2.69, 95% CI=2.3-3.14, p<.001) than heterosexuals who did not use MC. Sexual minority and heterosexuals who use MC report the same degree of general health (30% "fair to poor" and 70% "good to excellent"; aOR=.96, 95% CI=.43-2.14, p=.924). Sexual minorities and heterosexuals who use MC have similar rates of CUD (33% vs 27%, aOR=1.6, 95% CI=.75-3.49, p=.214).
Conclusions: Sexual minorities have more physical and mental illness than heterosexuals and are more likely to use MC. However, sexual minorities who used MC report similar physical, mental, and general health as heterosexuals who use MC. Lifetime CUD occurs in similar rates in both MC populations.

OPIOID AND STIMULANT USE AMONG BLACK SEXUAL MINORITY MEN: A LIFE COURSE PERSPECTIVE

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Behavior
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Efforts to reduce HIV and drug abuse among Black sexual minority men (BSMM) throughout the U.S. are urgently needed. Generational differences in drug use trends and HIV/AIDS epidemics may have created different risk trajectories for BSMM. The purpose

of this study is to explore age-related differences in the profiles, motivations, and contexts of opioid and stimulant use among BSMM.
Methods: In-depth qualitative interviews were conducted among 30 BSMM in Baltimore, MD from December 2018 to March 2019. Volunteers were recruited using active and passive strategies. Thematic analysis was conducted guided by Life Course theoretical domains.
Results: Participants' ages ranged from 25-63 (mean age 41, SD=12.4); 12 were under the age of 35, 18 were age 35 and older. Most (63.3%) reported an annual income of $20,000 or less; 86.7% were living with HIV. Older BSMM reported greater heroin/injection drug use; younger BSMM reported greater prescription painkiller use. In in-depth interviews, older BSMM attributed drug use initiation to social trends and sexual partners; younger men shared that prescription painkiller use led to misuse to address emotional pain. Across age groups, childhood sexual abuse impacted drug use initiation and persistence. Other major life events along the life course also increased BSMM's vulnerability to opioid and stimulant use as a coping strategy.
Conclusions: Social and developmental contexts influenced drug use initiation among BSMM with distinct effect in the older and younger group. Drug abuse and HIV interventions should support changes in individual behaviors, mental health services, and trauma-informed care models for BSMM of different age groups.

INHALANTS AND LGBT+ POPULATION: A NATIONAL EPIDEMIOLOGIC ANALYSIS

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Abstract Detail: Human
Drug Category: Other, Inhalants
Topic: Epidemiology
Abstract Category: Original Research
Designation: M.D., M.S.

Abstract: Aim: Inhalants are commonly used by the LGBTQI+ population, thus vulnerable to their negative consequences such as cardiac problems, dizziness, seizures, and decreased level of consciousness. US epidemiologic data on inhalants are scarce. The aims of this study are: to investigate associations between inhalant use and sexual identity groups and to investigate associations between inhalants with other substances (marijuana, tobacco, alcohol, illicit drugs, and psychotherapeutics) among lesbian/gays (LGs) who use inhalants.
Methods: Data came from the 2015-2017 NSDUH (n=128,679). Participants aged 18 or older were asked if they had used any inhalants in their lifetime, past-year, and past-month. We investigated the associations between inhalant use and sexual identity categories heterosexual, LGs, bisexual (Bs), and don't know/refused using survey-weighted logistic regression models adjusted by age, gender, race/ethnicity, education level, urbanicity, and survey year.
Results: Prevalences of lifetime, past-year and past-month use of inhalants were 9.4%, 0.5%, and 0.2%. LGs and Bs had higher odds of lifetime (LG: aOR=3.71, 95%CI=[3.08,4.47]; B: aOR=1.80, 95%CI=[1.62,2.01]), past-year (aOR=11.71, 95%CI=[8.74,15.69]; B: aOR=2.57, 95%CI=[1.90,3.47]), and past-month (aOR=19.89, 95%CI=[12.02,32.93]; B: aOR=3.19, 95%CI=[1.78,5.70]) inhalant use compared to heterosexuals. Among LGs: men had higher odds of lifetime (aOR=4.28, 95%CI=[3.04,6.01]), past-year (aOR=23.79,

95%CI=[9.17,61.72]) and past-month use (aOR=21.31, 95%CI=[6.25,72.60]) of inhalants compared to women; use of marijuana (aOR=2.73, 95%CI=[1.17,6.34]) and illegal drugs (aOR=3.86, 95%CI=[2.08,7.15]) were associated with past-year use of inhalants; past-month binge drinking (aOR=2.31, 95%CI=[1.10,4.87]) was associated with past-month use of inhalants.
Conclusions: LGBTQ+ population is at higher risk of inhalant use and concurrent use with other drugs as compared to heterosexuals.

KAPPA

BEHAVIORAL PHENOTYPES AND PET STUDIES OF KAPPA OPIOID RECEPTORS IN SOCIALLY HOUSED FEMALE AND MALE MONKEY MODELS OF COCAINE ABUSE

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Abstract Detail: Animal Study
Drug Category: Stimulants
Topic: Behavior
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: The kappa opioid receptor (KOR) system and its endogenous ligand, dynorphin, are implicated in the regulation of aversive states, stress, and substance abuse. The aim of this study is to extend the investigation of the dynorphin/KOR system using a homologous nonhuman primate model of cocaine use disorder (CUD) involving cocaine self-administration (SA) in socially housed female and male monkeys.
Methods: This ongoing study utilizes socially housed male and female cynomolgus monkeys (N=16/sex), some experimentally naïve at the start of the study and others with a cocaine SA history. Naive monkeys were trained under a 1- vs. 3-food pellets delay discounting choice procedure and the other monkeys under a cocaine (0.01-0.1 mg/kg/inj) vs. food (1-pellet) delay discounting choice procedure. The primary dependent variable was indifference point (IP) or the delay that results in 50% choice. In all monkeys, executive function was assessed using two different cognitive tasks utilizing CANTAB systems. Finally, all naive monkeys received a [11C]EKAP PET scan.
Results: Preliminary data indicates that when a low, non-preferred, cocaine dose was available and food was delayed, dominant females had higher IPs (more impulsive) compared to dominant males. Preliminary comparisons suggest no relationship between IP and errors under various cognitive tasks. The PET data are currently being analyzed.
Conclusions: A recent PET study with a novel KOR agonist tracer [11C]EKAP in humans reported that lower social status was associated with higher KOR availability in "anti-reward"/stress brain regions (Matuskey et al. 2019) and a correlation with cocaine choice in CUD subjects (Martinez et al. 2019). As it relates to behavioral phenotypes involving delay discounting and measures of executive function, data from the present study indicate non-

overlapping cognitive domains that, along with PET data, may prove to be sensitive biomarkers for decreasing cocaine SA.

MULTIFUNCTIONAL MU- AND KAPPA-OPIOID RECEPTOR LIGANDS AS POTENTIAL THERAPEUTICS FOR PAIN AND SUBSTANCE ABUSE

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Abstract Detail: Animal Study
Drug Category: Opiates/Opioids
Topic: Behavior
Abstract Category: Original Research
Designation: B.S.

Abstract: Aim: Multifunctional opioids, possessing activity at more than one receptor, may counter pain and substance use disorder (SUD) with fewer undesired side effects. We hypothesized that multifunctional opioids displaying a mixture of mu- (MOR) and kappa-opioid receptor (KOR) agonist and KOR antagonist activity would produce antinociception and efficacy against drug-seeking behavior without respiratory depression or place conditioning effects.
Methods: Analogs of the macrocyclic tetrapeptide natural product CJ-15,208 (cyclo[Phe-D-Pro-Phe-Trp) were screened for multifunctional MOR and KOR agonism and KOR antagonism in the 55oC warm-water tail-withdrawal test with wild-type C57BL/6J and knockout (KO) mice (n=8/dose) for the MOR, KOR or delta-opioid receptors (DOR). Liabilities of respiratory depression, hyperlocomotion, sedation (n=12/dose) and conditioned place preference (CPP; n=24/dose) were assessed. Selected analogs were further assessed for the ability to prevent reinstatement of drug-seeking behavior in the CPP and two-bottle choice (TBC) assays.
Results: Several promising analogs demonstrated antinociception after intracerebroventricular (i.c.v.) administration equivalent to morphine (ED50=2.35 (1.13-5.03) nmol), with subsequent KOR antagonist activity for 2-8 hours. Testing in KO mice demonstrated that the analogs produced antinociception through varying ratios of MOR/KOR agonism. Selected analogs prevented drug- and stress-induced reinstatement of extinguished drug-conditioned place preference (CPP), and also prevented stress-induced potentiation of voluntary morphine consumption in the TBC paradigm. Notably, all analogs tested directly demonstrated negligible respiratory or locomotor effects and lacked conditioned place preference or aversive properties in wild-type mice. Elimination of multifunctional activity by testing in opioid receptor knock-out mice restored liabilities consistent with the remaining receptor.
Conclusions: Aside from demonstrating efficacious antinociception, these analogs demonstrated improved liability profiles attributed to multifunctional activity at both KOR and MOR. Moreover, these data suggest the promise of multifunctional MOR/KOR compounds to safely treat pain as well as substance abuse and relapse in abstinent subjects.

PYRROLIDINEQUINOXALINE AND PYRROLIDINE-PYRANOPIPERAZINE ANALOGS CHARACTERIZED AS NOVEL KAPPA OPIOID RECEPTOR AGONISTS: IN VITRO RECEPTOR BINDING AND SIGNALING CHARACTERIZATION

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Abstract Detail: Animal Study
Drug Category: Stimulants
Topic: Chemistry
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Despite extensive efforts, no potential medicinal therapeutics for cocaine addiction have received FDA approval. The kappa opioid receptor system (KOR) is a potential therapeutic target, but available KOR ligands have not proven suitable. Our aim is to explore novel specific KOR agonist scaffolds, specifically the previously described 3,4 dichlorophenylacetamide-3-(N)-pyrrolidinequinoxaline (PAPQ) as well as the novel 3,4 dichlorophenylacetamide-3-(N)-pyrrolidine-pyranopiperazine (PAPPP) scaffold recently developed by our laboratory, for the development of analogs with unique KOR signaling properties.
Methods: Compounds with 4-N substitutions of the PAPQ and PAPPP scaffolds were designed by our team and synthesized by Wuxi Apptech. All compounds were dissolved in DMSO (20 mM), with separate aliquots used for each assay. Dose response curves were used to obtain binding potency via displacement of [3H]U69,593, as well as activation potency and efficacy of stimulation of [35S]GTPγS binding were performed with cell membranes prepared from U2OS-expressing cells (DiscoverX). Beta-arrestin-2 signaling was assessed using fusion protein coupling and enzymatic amplification of a chemiluminescent substrate in intact cells, with determination for each compound of activation potency and efficacy compared to the reference compound U69,593.
Results: Eighteen novel PAPQ and 34 PAPPP analogs were synthesized and tested. In terms of potency, 11 of the PAPQ compounds and 13 of the PAPPP compounds had both IC50 in [3H]U69,593 binding and EC50 in [35S]GTPγS stimulation assays below 20 nM. Of these, 1 of the PAPQ compounds and 5of the PAPPP compounds demonstrated substantial bias for G-protein signaling over arrestin signaling.
Conclusions: We have generated over 50 novel analogs, several of which have high potency. Of particular interest, the biased kappa compounds with high potency in vitro may have reduced side effects in vivo, which may enhance their therapeutic potential. Further in vivo studies are warranted.

Neuroimmune

IMPACT OF ALCOHOL USE DISORDER AND ITS TREATMENT ON GUT PERMEABILITY, MICROBIAL TRANSLOCATION, AND SYSTEMIC INFLAMMATION AMONG PEOPLE LIVING WITH HIV

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Abstract Detail: Human
Drug Category: Alcohol
Topic: HIV/Immune
Abstract Category: Original Research
Designation: M.D.

Abstract: Aim: Alcohol consumption worsens gut permeability among people living with HIV (PLHIV) and may drive chronic immune activation leading to poor outcomes. We hypothesized that PLHIV and alcohol use disorder (HIV+/AUD+) would exhibit increased gut permeability, microbial translocation, and immune activation compared to PLHIV without substance use disorder (HIV+/SUD-), and that pharmacologic treatment of AUD would be associated with reductions in relevant biomarkers.
Methods: Cryopreserved plasma collected from HIV+/AUD+ participants of both sexes, enrolled in CHOICES CTN-0055 (N=23; sampled at enrollment and 1-month AUD treatment) and HIV+/SUD- individuals (N=20; sampled at enrollment) was used to quantify: intestinal-fatty-acid-binding-protein (I-FABP), soluble CD14 and CD163 (sCD14; sCD163), soluble CD40L (sCD40L), lipopolysaccharide-binding-protein (LBP), and TLR-4 ligands (HEK-Blue hTLR4 reporter cells).
Results: CD4+ T cell counts were comparable between HIV+/AUD+ and HIV+/SUD- participants [664 cells/µl (±287) versus 604 cells/ µl (±304), $p > 0.05$)]. VL was undetectable in 95% of both cohorts. HIV+/AUD+ individuals exhibited higher TLR-4 ligands (median 766 pg/ml; IQR 577-1100), I-FABP (median 1697 pg/ml; IQR 986-2409), LBP (4513 ng/ml, IQR 3368-6813), and sCD40L (median 1302 pg/ml; IQR 1010-1924) at enrollment compared to HIV+/SUD- individuals (TLR-4 ligand median 449 pg/ml, IQR 346-623, p=0.0008; I-FABP median 1259 pg/ml, IQR 824-1784, p=0.058; LBP 3559 ng/ml, IQR 2893-4869, p=0.062; sCD40L median 849 pg/ml, IQR 608-1215, p=0.0019; Mann-Whitney). Following 1-month AUD treatment, declining I-FABP (median 1089; IQR 829-1900; p=0.060), and TLR-4 ligands (median 675; IQR 540-986; p=0.13, Wilcoxon matched-pairs signed test) were observed.
Conclusions: Among PLHIV, AUD is associated with increased gut permeability, microbial translocation, and T-cell activation. One month of AUD treatment was associated with reduction in a biomarker of gut permeability; robust reductions in biomarkers of systemic immune activation and microbial translocation were not observed. On-going investigations will determine how AUD and its treatment impact cellular immune phenotypes and function.

TRANSLOCATOR PROTEIN BINDING IN THE BRAIN: A PET STUDY OF METHAMPHETAMINE USE DISORDER

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Abstract Detail: Human
Drug Category: Stimulants
Topic: Substance Use Disorder
Abstract Category: Original Research

Designation: M.S.

Abstract: Aim: The translocator protein 18 kDa (TSPO) is found mainly on the outer mitochondrial membrane, showing increased expression in activated microglia. TSPO expression therefore is considered an index of neuroinflammation. It is elevated in the brains of rats following chronic methamphetamine treatment, and of humans who have used methamphetamine chronically and then were abstinent for 0.5-4 years. The goal of this study was to compare TSPO binding in the brains of individuals with current Methamphetamine Use Disorder (MUD) to controls of comparable age, sex and tobacco use. Other factors typical of MUD (e.g., D2 dopamine receptor deficits, depression) were also compared between groups.
Methods: We used positron emission tomography with the radiotracers [11C]DAA1106 and [18F]fallypride to measure TSPO and dopamine D2-type receptor binding, respectively, in MUD participants (n=11) and healthy controls (n=12). MUD participants were methamphetamine-abstinent ≥4 days; and all participants had negative urine drug tests and had abstained from smoking or using nicotine-containing products for ≥12 h before PET scanning.
Results: MUD participants had typical characteristics: tobacco smokers with elevated depression ($p<0.0001$), anxiety ($p=0.002$), difficulties in emotional regulation ($p=0.012$), and lower striatal dopamine D2-type receptor availability vs. controls ($p=0.021$). General Linear Mixed Model analysis found no significant main effect of group on TSPO binding across brain regions ($p>0.05$), but an interaction between group and region ($p<0.0001$). In post-hoc analyses, the standardized uptake values for [11C]DAA1106 in MUD participants were above control in the parietal ($p=0.034$), anterior cingulate ($p=0.005$), dorsolateral prefrontal ($p=0.001$) and dorsomedial prefrontal ($p=0.026$) cortices, but not other brain regions (p's>0.05).
Conclusions: These findings suggest that methamphetamine use produces neuroinflammation in the cerebral cortex, and that medications targeting neuroinflammation may help MUD patients who are recently abstinent, as most are when they begin treatment.

ACUTE ABUSE-LIKE EXPOSURES TO TOLUENE INCREASES EXPRESSION OF PATHOLOGICAL MARKERS IN THE LUNG AND BRAIN

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Abstract Detail: Animal Study
Drug Category: Other, Inhalant Abuse & Toxicology
Topic: Other
Abstract Category: Original Research
Designation: B.A.

Abstract: Aim: Toluene is a volatile organic compound that is commonly abused by young adolescents for its central nervous system depressant-like effects. While previous research has demonstrated that toluene has neurobehavioral effects, little is known about toluene's toxicological effects in the lungs and brain.
Methods: The present study characterized the toxicological effects of acute toluene exposure in the lungs and brains of male Swiss-Webster mice (N = 68). Using a static gas chamber, mice (PND 28) were randomly exposed to a single 30 min toluene exposure (0 ppm, 1000 ppm, 2000 ppm, or 4000 ppm). Lung and brain tissue were extracted 24 hours after toluene exposure to

be analyzed using histology and immunohistochemistry. Hematoxylin and eosin stained samples were assessed for increases in dense cellular architecture and signs of inflammation and rated on a four-point scale (0 = no pathology to 4 = severe pathology).
Results: Histology results revealed a significant main effect of exposure condition on pathology in lung tissue ($p = .04$) with the 2000 and 4000 ppm exposures expressing greater signs of pathology than control (p's $< .05$). Lung tissue will be further assessed for increases in macrophage expression, cellular proliferation, neutrophil and lymphocyte count, and changes in vasculature. Additionally, brain tissue will also be analyzed for signs of apoptosis, oxidative stress, and astrocyte damage.
Conclusions: The increased signs of inflammation and cellular damage suggest that a single high concentration exposure to toluene is capable of producing pathological changes in lung tissue and possibly brain. Overall, inhalant abuse may have previously unconsidered pathological and clinical implications after even a single use.

Sleep/Medical Consequences

SLEEP DISTURBANCE AS PREDICTOR OF COGNITIVE-BEHAVIORAL THERAPY OUTCOMES IN INNER-CITY ADULTS WITH POST-TRAUMATIC STRESS AND SUBSTANCE USE DISORDERS

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Abstract Detail: Human
Drug Category: Polydrug (i.e. Use of more than one drug combination)
Topic: Treatment
Abstract Category: Original Research
Designation: M.A.

Abstract: Aim: The co-occurrence of posttraumatic stress disorder (PTSD) and substance use disorders (SUD) is highly prevalent and difficult-to-treat. A behavioral mechanism of clinical relevance to these associations is sleep disturbance. We hypothesized that greater sleep disturbance at baseline (pre-treatment) would predict (a) greater end-of-treatment PTSD severity and (b) higher levels of substance use during a 12-week cognitive-behavioral treatment program.

Methods: Participants included 53 inner-city adults meeting at least four symptoms of DSM-5 PTSD and current (DSM-IV) substance dependence (51% women; 75.5% African American; Mage=45.42, SD=9.99). Hierarchical regression models were employed. Treatment condition, baseline PTSD symptom severity, number of SUD diagnoses at baseline, and craving for drug of choice at baseline were covariates; baseline sleep disturbance (Pittsburgh Sleep Disturbance Questionnaire total score) was the predictor.
Results: Sleep disturbance did not predict end-of-treatment PTSD severity (CAPS-5; β=-.023, p= .871). Greater baseline sleep disturbance predicted higher levels of substance use during treatment. Specifically, greater baseline sleep disturbance predicted number of substances used at session 1 per urinary drug screen (UDS; β=.371, p=.012), shorter longest sustained abstinence for drug of choice (Time-Line Follow-Back [TLFB]; β=-.291, p=.05), and there was

a trend for sleep disturbance predicting substance abstinence at session 12 (TLFB; β=-.366, p=.058).
Conclusions: These results provide preliminary evidence that sleep disturbance may impact substance use during the course of a 12-week cognitive-behavioral treatment program. Sleep-based interventions may be fruitful in improving PTSD/SUD treatment outcomes. These findings contribute to the relative dearth of information regarding the association of sleep disturbance with PTSD/SUD treatment outcomes in the context of a cognitive-behavioral treatment program.

THE ASSOCIATION BETWEEN SLEEP DISTURBANCE AND OPIOID USE

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Substance Use Disorder
Abstract Category: Original Research
Designation: B.A.

Abstract: Aim: This study assessed the hypothesis that increased sleep disturbance is associated with increased opioid use in treatment-seeking patients.
Methods: Patients being admitted to a residential rehabilitation program for opioid use were asked for voluntary participation in a survey. Questions included a modified Brief Addiction Monitor (BAM) which assessed past 30-day substance use and symptoms associated with opioid use disorders (OUD). Responses were rated on Likert scales or binned numbers of the past 30-days and were analyzed using ordinal regression to examine the relationships between sleep disturbance and the severity and symptoms of opioid use. Sleep disturbance was evaluated as the number of past 30-days the participant had difficulty falling asleep.
Results: A sample of 364 patients completed the survey. Participants were primarily male (73%) and white (93%), with 32% unemployed at time of admission. The ordinal regression demonstrated an association between self-reported sleep disturbance and opioid use in the past 30 days ($p=0.028$). Sleep disturbance was also found to be associated with dysphoric mood which included feelings of depression, anxiety, and anger ($p<0.001$).
Conclusions: These data suggest that sleep disturbance is associated with opioid use and dysphoric mood. Sleep is known to have a bidirectional relationship with mood, but in the context of opioid use, has additional significance as both insomnia and dysphoric mood are common symptoms of opioid withdrawal. It is possible that opioid use and sleep disturbance represent a dose-dependent exacerbation of withdrawal symptoms, which can be further complicated by dysphoric mood. It may also suggest that insomnia is a prevalent existing symptom in opioid users that induces opioid use and dysphoric mood, raising the question of whether treating underlying symptoms could reduce relapse in persons with OUD. Altogether, results support additional and targeted research on OUD and sleep.

ILLICIT SUBSTANCE USE HISTORY PREDICTS INCREASED ALLOSTATIC LOAD: CROSS-SECTIONAL EVIDENCE FROM A MAINTENANCE CLINIC POPULATION

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Abstract Detail: Human
Drug Category: Polydrug (i.e. Use of more than one drug combination)
Topic: Tolerance/Dependence
Abstract Category: Original Research
Designation: B.A., B.S.

Abstract: Aim: Allostatic load (AL), an operationalization for cumulative strain on physiology from adaptation to stress over a lifetime, can damage cardiovascular, neuroendocrine, and metabolic systems. Our aim was to evaluate AL in the context of drug use, including alcohol use. We hypothesized that after controlling for age and other potential confounds, people with lengthier histories of drug use would have higher AL scores.
Methods: Participants were 751 adults tested cross-sectionally in either of two studies at our clinic, one enrolling opioid users who sought treatment, the other enrolling any adult who consented (regardless of drug-use status). Mean age was 37.74 years (18-66); 472 (62.85%) participants were male, and 562 (74.83%) were African American. AL was operationalized as a 12-biomarker panel based on measures most frequently used in AL literature without requiring 24-hour urine collection or overnight laboratory stays. A continuous AL score was generated for each participant using canonically scaled z-score summation, and multiple regression was used to predict AL from drug-use histories while controlling for age, race, gender, and attained education level.
Results: The multiple regression model was significant overall ($F(10,740)=19.97$, $p<2.2E-16$) with $R2=0.21$. Lengthier opioid ($\beta=0.23$, 95%CI [0.16, 0.30]) and cocaine ($\beta=0.12$, 95%CI [0.05, 0.20]) use histories significantly predicted increased AL. African American race ($\beta=0.10$, 95%CI [0.03, 0.16]), perceived stress ($\beta=0.18$, 95%CI [0.10, 0.25]), poorer sleep quality ($\beta=0.08$, 95%CI [0.01, 0.15]), and greater alcohol consumption ($\beta=0.08$, 95%CI [0.01, 0.15]) were also significant predictors of increased AL.
Conclusions: This study provides novel cross-sectional evidence from a clinical sample for the relationship between drug dependence and allostatic load, independent of age and other potential contributors. This finding suggests that extended drug use, in the contexts studied here, can exacerbate the accumulation of stress-related physiological damage that accompanies aging.

SLEEP OUTCOMES AND COCAINE USE DISORDER SEVERITY AMONG COCAINE USERS AND COCAINE AND CANNABIS CO-USERS

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Abstract Detail: Human
Drug Category: Polydrug (i.e. Use of more than one drug combination)
Topic: Other
Abstract Category: Original Research
Designation: M.S.

Abstract: Aim: Sleep problems are common among chronic cocaine users (Angarita, Emadi, Hodges, & Morgan, 2016). Research suggests some cocaine users combine cocaine and cannabis to improve sleep quality and reduce cravings (Gonçalves & Nappo, 2015). However, combining cocaine and cannabis may contribute to sleep disturbances (Schierenbeck, Riemann, Berger, & Hornyak, 2008). Given these mixed findings, the current study compared the severity of drug use and sleep outcomes among cocaine users (COC only) and cocaine and cannabis co-users (COC+THC).
Methods: Data were derived from baseline measures of an ongoing randomized clinical trial (R01DA043938; PI: Stoops). The preliminary sample consists of 68 participants and is predominantly African American (76.5%) with a mean age of 51.49 (SD=9.29). Cocaine and cannabis use were determined by urinalysis. Cocaine use disorder (CUD) severity was determined by the number of DSM-5 criteria met for CUD. Sleep outcomes were assessed using the St. Mary's Hospital Sleep Questionnaire (Ellis et al., 1980). One-way ANOVA were used for hypothesis testing.
Results: Overall, COC+THC users reported significantly higher CUD severity compared to COC only users [$F(1, 63)=4.93$, $p=0.030$]. Preliminary ANOVA indicate a statistically significant difference in the amount of sleep per night between COC+THC users and COC only users [$F(1, 66)=5.48$, $p=0.022$], with COC+THC users sleeping 90 minutes less per night on average. However, perceived sleep quality and daytime alertness do not differ significantly between groups.
Conclusions: Cocaine and cannabis co-users may perceive their sleep to be of similar quality as cocaine-only users despite lower sleep duration and higher CUD severity. Implications for sleep treatment for cocaine users will be discussed. Assessing interactions between cocaine and cannabis use may aid in efforts to improve sleep and drug use outcomes.

SOCIAL JETLAG AND DRUG USE DURING OPIOID AGONIST TREATMENT FOR OPIOID USE DISORDER: POTENTIAL SEX DIFFERENCES

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Treatment
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Mismatches between daily life obligations and preferred timing of sleep/wake (i.e., chronotype, CT) can lead to the circadian sleep disorder "social jetlag." Late CT and social jetlag have been associated with drug use in general population samples, but not, to our knowledge, within a sample of people with substance use disorders. We hypothesized that late CT and social jetlag would be positively associated with drug use during opioid use disorder treatment.
Methods: 233 outpatients (49 women, 184 men) receiving methadone or buprenorphine treatment completed the Munich Chronotype Questionnaire. All participants self-reported their CT (categorized as early/normal/late). For the subset (n = 72; 14 women, 58 men) who reported

working, social jetlag was calculated as the difference between self-reported midsleep times on free-days vs. workdays. Drug use was assessed by twice- or thrice-weekly urinalysis. Participants were classified as having high drug use (HDU), low/no drug use (LDU), or as dropping out of treatment (DOT), using cluster analysis of their opioid- and cocaine-urinalysis results.
Results: Participants of all CTs had statistically significant social jetlag (i.e., > 0 hours); jetlag amount did not differ among CTs. Compared to early CT participants, late CT participants were more likely to be in the HDU or DOT clusters. Differences in social jetlag among treatment-outcome clusters depended partly on participants' sex. Female, but not male, DOT participants unexpectedly reported less social jetlag than LDU or HDU participants. Female LDU and HDU participants also reported more social jetlag than male LDU and HDU participants, respectively.
Conclusions: Late chronotype may be a risk factor for poor treatment outcomes: more drug use and dropping out. The sex differences we found need to be replicated, but, for women, less social jetlag could be a counterintuitive risk factor for dropout, perhaps related to free/unstructured time during the day.

CURRENT SMOKING AS A MARKER OF A HIGH-RISK PROFILE AFTER MYOCARDIAL INFARCTION

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Abstract Detail: Human
Drug Category: Nicotine/Tobacco
Topic: Behavior
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Continued smoking following myocardial infarction (MI) is strongly associated with increased morbidity and mortality. However, many patients after MI continue to smoke. Patients who smoke may also engage in other behaviors that put them at high-risk of subsequent events. This study sought to characterize the risk profile of post-MI patients who currently smoke.
Methods: Data were taken from the 2017 Behavioral Risk Factor Surveillance Survey. 4.2% of the sample (N=26,004) reported having been diagnosed with an MI. Patients reporting past MI were classified by smoking status (current vs. former/never) and compared on comorbidities, measures of physical health, and health-related behaviors. Attendance at cardiac rehabilitation (CR) (queried in a subset of states, N=2130) was examined by smoking status. Initial analyses are based on univariate outcomes that disregard the complex survey design.
Results: Current smoking was significantly higher in those with past MI (22.3% vs. 15.2%). Among post-MI patients, individuals reporting current smoking were also more likely to report other medical comorbidities such as history of stroke (23.2% vs. 18.9%) or COPD (42.8% vs. 21.3%). They were less likely to report taking blood pressure (86.8% vs. 92.4%) and cholesterol medications (78.9% vs. 86.1%). Current smokers were more likely to report fitness-related difficulties (53.4% vs. 41.6%) and less likely to eat ≥1 vegetable per day (75.8% vs. 81.0%). Within the subsample queried about CR, 45% reported attending at least some

rehabilitation following their MI, but attendance was significantly lower in current smokers (36.2% vs. 47.5%).
Conclusions: Current smoking is a marker for a high-risk profile within the post-MI population. Current smokers frequently have multiple comorbidities that would improve with quitting and struggle with various health-related behaviors that put them at further risk. They are also less likely to engage in secondary prevention. Current smoking should be considered a marker for a high-risk profile within cardiac patients.

Trauma

HIGH RATES OF CHILDHOOD AND LIFETIME TRAUMA AND CHRONIC STRESS IN CANNABIS USERS, AND THE RELATED SEX/GENDER DIFFERENCES

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Abstract Detail: Human
Drug Category: Marijuana/Cannabinoids
Topic: Substance Use Disorder
Abstract Category: Original Research
Designation: M.D.

Abstract: Aim: Higher rate of cannabis use in individuals with chronic stress and trauma has been reported in few available studies, but there is lack of evidence on the characteristics of trauma and the potential sex/gender differences.
Methods: This is a cross sectional study of 840 individuals recruited between 2007 and 2012 from community in New Haven, Connecticut. The Cumulative Adversity Index (CAI) was used to measure cumulative lifetime trauma, major life events, and chronic stress. Childhood Trauma Questionnaire (CTQ) was used to measure childhood trauma. Current and regular use of drugs were assessed using self-report questionnaires.
Results: History of childhood abuse was significantly higher in cannabis users (41.7%) compared to non-users (34.2%) (p-value: .047). Cannabis users also had higher number of trauma (.85 vs. .63, p-value .039) and higher total scores of CTQ (38.89 vs. 35.93 , p-value .017), compared to non-users, which remained significant after controlling for demographic factors and use of other drugs. However, when we analyzed men and women separately, the associations between cannabis use with childhood trauma were only significant in women, not in men. Compared to non-cannabis users, cannabis users reported higher rates of major life events with longer duration. Cannabis users also reported higher rate of cumulative traumatic events and chronic stress (p-value<.01). Overall, the total score of CAI was higher in cannabis users compared to non-cannabis users (24.79 vs. 19.58, respectively, p-value<.001). Moreover, cannabis use also had a significant negative association with age of subjects at the time of first life event (p-value<.05).
Conclusions: There is a higher rate of childhood trauma in women who regularly use cannabis, and higher rates of lifetime trauma, major life events, and chronic stress in all regular cannabis users, compared to non-users. Trauma, cumulative adversity, and stressors may play a significant role in cannabis use and development of cannabis use disorders.

COMORBID ALCOHOL, TOBACCO, AND OTHER MENTAL HEALTH DISORDERS AND ASSOCIATIONS WITH SEXUAL ORIENTATION AND MINORITY STRESS

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Abstract Detail: Human
Drug Category: Alcohol
Topic: Substance Use Disorder
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Sexual minorities are at increased risk for tobacco use disorder (TUD), alcohol use disorder (AUD), and other mental health disorders. However, it is not known if comorbidities of these are also higher among sexual minorities. This study examined mental health comorbidities and whether minority stress-related factors were predictive of comorbidity.
Methods: We used data from the nationally-representative NESARC-III survey to examine the prevalence of the co-occurrence of past-year TUD or past-year AUD with past-year (1) anxiety disorders, (2) mood disorders, or (3) post-traumatic stress disorder (PTSD) among heterosexual, bisexual, and gay/lesbian individuals (n=35,796). Then, among those who identified as sexual minorities (n=3,203), we examined minority stress-related correlates of comorbidity status including sexual orientation discrimination, social support, stressful life events, and adverse childhood experiences (ACEs).
Results: Among those with a past-year AUD, 34% had a mental health comorbidity (non-PTSD anxiety disorder, mood disorder, or PTSD). More than half of bisexual (55%) and gay/lesbian (51%) individuals had a mental health comorbidity, while only one-third of heterosexual individuals with a past-year AUD had a mental health comorbidity. Comorbidities were particularly high among bisexual women (61%). Among those with past-year TUD, 36% had a mental health comorbidity. Only one-third (35%) of heterosexual individuals with a TUD had a mental health comorbidity. Again, bisexual individuals with a TUD had the highest prevalence of a mental health comorbidity (66%). Among sexual minorities, frequency of sexual orientation discrimination (significant aOR range=1.08-1.10), number of stressful life events (significant aOR range=1.25-1.43), and ACEs (significant aOR range=1.04-1.18) were associated with greater odds of comorbidities. Greater social support was inversely associated with TUD comorbidities (significant aOR range= 0.96-0.97).
Conclusions: This research suggests integrated substance use and mental health prevention and treatment programs are needed particularly for sexual minorities. Stressors experienced by sexual minorities may be important drivers of these high levels of comorbidities.

SEX DIFFERENCES IN REWARD AND ATTENTION NEUROCIRCUITRIES AMONG INDIVIDUALS WITH POSTTRAUMATIC STRESS DISORDER AND SUBSTANCE USE DISORDER

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Abstract Detail: Human
Drug Category: Other, General substance use (alcohol and other substances)
Topic: Neurobiology
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Posttraumatic Stress Disorder (PTSD) and Substance Use Disorder (SUD) are highly comorbid mental health problems that are associated with severe functional impairment. PTSD and SUD share underlying pathophysiology, and disrupted reward and emotion processing are common to both disorders. Further, the neural dysfunction associated with PTSD and SUD may differ by sex. In comparison to men, women are at greater risk of developing PTSD following trauma and demonstrate differential responses to substances of abuse in brain regions associated with reward and emotion processing. Understanding sex differences with regard to potential synergistic effects of PTSD- and SUD-related neural dysfunction may help advance individualized prevention and intervention efforts.
Methods: The sample is comprised of N=43 adults (males and females; 42% females) with co-occurring PTSD and SUD. Measures included clinician-rated PTSD severity, self-report alcohol use disorder (AUD) severity, and demographic information. Task-based functional magnetic resonance imaging (fMRI) was conducted. The fMRI task involved audio presentation of individualized imagery scripts, consisting of 2-min trauma-related, substance-related, and neutral scripts. Whole-brain analyses were used to examine associations between BOLD response to audio scripts (3 conditions as described above), PTSD severity, AUD severity, and demographic information. A group-level, mixed-effects generalized linear model was conducted.
Results: Greater PTSD severity was associated with increased BOLD response to substance-related (versus trauma) audio scripts in dorsolateral prefrontal cortex, anterior cingulate cortex, insula, caudate, and superior temporal gyrus (initial threshold $p<.002$, cluster corrected $p<.05$). This effect was apparent in females, but not males.
Conclusions: Although preliminary, these findings indicate that PTSD severity may be differentially related to neural responses to substance-related cues among females versus males. Future work is needed to replicate these findings and examine how sex differences relate to clinical correlates for individuals with PTSD and SUD.

PREDICTORS OF PARTICIPANT ACCEPTABILITY OF A MINDFULNESS-BASED INTERVENTION FOR WOMEN IN SUBSTANCE USE DISORDER TREATMENT

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Abstract Detail: Human
Drug Category: Polydrug (i.e. Use of more than one drug combination)
Topic: Treatment

Abstract Category: Original Research
Designation: B.A.

Abstract: Aim: To assess the predictors of acceptability of a 12-session mindfulness-based intervention (Moment-by-Moment in Women's Recovery, MMWR). Based on the theoretical framework of acceptability, we hypothesized 1) time in treatment prior to the start of the intervention would be positively associated with acceptability, 2) trauma severity would be negatively associated with acceptability, 3) mindfulness predisposition would be positively associated with acceptability, 4) these three variable would collectively predict acceptability, and 5) acceptability would predict application of mindfulness techniques at session 12.
Methods: The current analyses are based on data from 100 women randomly assigned to the MMWR condition in a randomized clinical trial. Participants were 60% Latina, 73% methamphetamine users, and 74% had a history of trauma. Acceptability was measured by three surveys: formal practice and informal practice both collected following session 3 and satisfaction collected following session 2.
Results: H1: no correlation between time in treatment and formal practice p=.25, informal practice p=.12, or satisfaction p=.09. H2: no correlation between trauma severity and formal practice p=.20, informal practice p=.28, or satisfaction p=.12. H3: a correlation between mindfulness predisposition and informal practice, r=.22 p=.05, but no correlation with formal practice p=.30, or satisfaction p=.64. H4: regression model predicting formal practice was significant, R2=.15,F(5,76)=2.65,p=.03 and the model predicting informal practice was significant, R2=.14,F(5,76)=2.55,p=.04, but the model predicting satisfaction was not significant, p=.37. H5: correlations between applied mindfulness and informal practice r=.26,p=04 and satisfaction, r=.26,p=.04, but not formal practice p=.09 and the regression model was not significant p=.14.
Conclusions: MMWR may benefit from adaptation to increase acceptability for those with low mindfulness predisposition because it was associated with informal practice and informal practice was associated with applied mindfulness. This study emphasizes the importance of developing practice and satisfaction early in the intervention to increase application of intervention techniques by the end of the intervention.

Vaping

JUUL USE IN SCHOOL: CROSS-SECTIONAL STUDY OF CT HIGH SCHOOL ADOLESCENTS

Asti Jackson[*1], Grace Kong[1], Ran Wu[1], Meghan Morean[2], Danielle Davis[1], Deepa Camenga[3], Dana Cavallo[1], Krysten Bold[1], Patricia Simon[1], Suchitra Krishnan-Sarin[1]*

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Abstract Detail: Human
Drug Category: Nicotine/Tobacco
Topic: Epidemiology
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: JUUL use is popular among youth and social media evidence suggests that adolescents use JUUL at school. The current study uniquely examines specific locations where youth use JUUL (and other e-cigarettes) at school.
Methods: Students from 6 Connecticut high schools in 2019 reported on past-month use (defined as ≥1 day of use in past 30 days) of the following e-cigarette device types: 1) JUUL, 2) any pod system other than JUUL, 3) Disposables, 4) Vape pens, and 5) Mods. Past-month users of a device who used a device in school in the past month reported on specific locations: class, bathroom, hallway/stairway, outside but on school grounds and other school locations. Separate binary logistic regression models predicted e-cigarette device use in each school location. Predictors included demographics (age, sex) and past month use of each device in school.
Results: Among past-month users, use rates in schools were: 45.5% (N=547) JUUL, 41% (N=219) other pods, 38.8% (N=118) of disposables, 34.4% (N=225) vape pens and 27.1% (N=81) mod. Across devices, use in bathrooms was the most endorsed location: 75.7% JUUL, 72.2% other pod, 80.5% disposables, 78.2% vape pens and 71.6% mod. Other school related locations category was the least endorsed: 8.6% JUUL, 10.5% other pods, 9.3% disposables, 8% vape pens and 10.5% mods. Models revealed that vape pens (p=.034) and disposables (p=.041) were used significantly in the hallway/stairway and JUULs (p=.040) were used significantly in the bathroom. No other differences by device type were found.
Conclusions: E-cigarette use in schools is commonly reported among high schoolers. School-wide efforts should be implemented to reduce e-cigarette use in locations widely reported across e-cigarette device users, such as bathrooms. Further investigation into adolescent use of JUULs, vape pens and disposable e-cigarette use in school is warranted.

PLASMA NICOTINE DELIVERY AND SUBJECTIVE EFFECTS OF PROTONATED NICOTINE LIQUIDS IN ELECTRONIC CIGARETTE USERS AND CIGARETTE SMOKERS

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Abstract Detail: Human
Drug Category: Nicotine/Tobacco
Topic: Behavior
Abstract Category: Original Research
Designation: B.A.

Abstract: Aim: Electronic cigarettes (ECIGs) produce an aerosol by heating a liquid that often contains nicotine that is sometimes freebase and sometimes protonated (salt). This study's purpose is to determine, in ECIG users and cigarette smokers, the effects of three concentrations of protonated nicotine liquid aerosolized at two different ECIG device power settings (measured in watts, W).
Methods: Twelve participants (nine men, three women; seven white; five cigarette smokers, seven regular ECIG users) with a mean age of 28 years (SD=10.9) completed six sessions that differed by liquid nicotine concentration (10, 15, or 30 mg/ml, protonated) and device power (15 or 30 W; SUBOX Mini). Plasma nicotine concentration and subjective effects were

measured before and after participants took 10 puffs in each condition (30 sec inter-puff interval).
Results: Preliminary analyses (ANOVA) show that plasma nicotine concentration increased with protonated nicotine concentration and device power. A significant device*time interaction was observed (ps < .05), with significantly increased plasma nicotine across all conditions after product use. The greatest mean (SD) plasma nicotine increases occurred in the higher-powered conditions, with 25.2 (7.45) ng/ml in the 30 mg/ml+30 W condition compared to 8.6 (2.54) ng/mL in the 10 mg/ml+15 W condition. For the subjective item "craving," a significant main effect of time was observed (p < .01), with decreased scores in all conditions following product use; the lowest scores were observed in the 30 mg/ml+30 W condition.
Conclusions: These results suggest that, as with freebase nicotine, protonated nicotine delivery is influenced by liquid nicotine concentration and device power. Regulations aimed at limiting nicotine delivery from ECIGs that use protonated nicotine can be informed by systematic evaluation of the effects of this form of this dependence-producing drug.

RISK FACTORS FOR VAPING MAY DIFFER BY MARIJUANA AND TOBACCO E-LIQUID USED

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Abstract Detail: Human
Drug Category: Marijuana/Cannabinoids
Topic: Adolescent
Abstract Category: Original Research
Designation: M.S.W., Other, Ph.D., Prof.

Abstract: Aim: Given the current public health emergency associated with vaping, increasing knowledge of risk factors for vaping and the use of specific e-liquids is of utmost importance. We aim to characterize college students who vape nicotine or marijuana and may be at risk of lung injury. We hypothesized that those who vape only marijuana were more likely to use other substances than those vaping only nicotine.
Methods: This secondary analysis of the 2018-2019 internet-based Healthy Minds Study (HMS; HM Network, 2019) characterizes college students from universities across the nation who were randomly selected to participate using e-mail, with probability weights to adjust for non-response. This analysis includes 36,170 students from 79 institutions who provided complete data related to past 30-day use of an electronic cigarette or vape pen and type of e-liquid used. SAS 9.4 was used for data analysis.
Results: Of the 16.8% college students reporting past 30-day vaping (6,088), 71%(4,309) only vaped nicotine and 15.7%(957) only marijuana. Those who endorsed vaping were significantly more likely (p<0.0001) to smoke tobacco and marijuana, drink alcohol, use other drugs and have mental health problems. Those who vaped marijuana were significantly more likely to be male, white, older, graduate students, live off-campus and be first generation college students. In the multivariate model, alcohol use (AOR= 1.82(95% CI 1.41,2.36) and other drug use (AOR=1.53(95% CI 1.20,1.95) increased vaping marijuana relative to nicotine, but not binge drinking (AOR=0.66(95% CI 0.55,0.81) or nonmedical prescription stimulant use (AOR=0.71(95% CI 0.64,1.17).

Conclusions: Risk factors for vaping among college students are similar to those for other drug use; risk for vaping marijuana, which has been shown to put people at risk for vaping or e-cigarette associated lung injury (VALI or EVALI), may be distinct from other e-liquids and prevention efforts need to be tailored appropriately.

DEVELOPMENT OF PARAMETERS FOR DELTA-9-TETRAHYDROCANNABINOL (THC) VAPOR EXPOSURE IN RATS: DOSE-EFFECT COMPARISONS BY SEX AND ROUTE OF ADMINISTRATION

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Abstract Detail: Animal Study
Drug Category: Marijuana/Cannabinoids
Topic: Sex Differences
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: The most common route of administration of cannabis and its constituents (e.g., Delta-9-tetrahydrocannabinol, THC; cannabidiol, CBD) in humans is inhalation. Advances in drug vapor exposure systems utilizing e-cigarette technology have enabled evaluation of THC vapor effects in laboratory animals. The purpose of this study was to 1) establish parameters of THC vapor exposure in rats sufficient to produce behavioral effects in a battery of tasks sensitive to THC; 2) to investigate sex differences in the effects of THC vapor and THC injection (intraperitoneal, i.p.) on these behaviors.
Methods: Male and female Wistar and Sprague Dawley rats (N=48, 12 per group) participated in a within subject design protocol in which all animals received all conditions. Vapor was delivered using custom vapor chambers systems (La Jolla Alcohol Research, Inc., LJARI). Conditions were THC i.p. (0-20 mg/kg) and passive THC vapor (0-200 mg/ml) delivered under conditions where puff duration (2-6s), puff frequency (5-20x), and total exposure (10-60m) were systematically varied. The behavioral battery included rectal measurements of body temperature, a tail-flick assay for nociception, and food-maintained operant responding.
Results: THC produced decreases in body temperature, increases in tail flick latency, and dose or exposure-related increases and decreases in food-maintained responding. THC vapor produced similar effects as those produced by THC i.p. injection. Sex differences emerged with respect to dose and the time course of THC effects; females showed greater sensitivity to THC than males.
Conclusions: These preliminary studies demonstrated THC vapor delivery produced reliable effects on body temperature, nociception, and food-maintained behavior, and established appropriate dosing and testing parameters for comparison with other cannabinoid constituents. Ongoing studies are also examining operant self-administration of THC vapor.

Oral Communications II, Q&A

Cannabis

CANNABIS AND GASTROINTESTINAL TRACT (GIT) ILLNESS: A PARADOX?

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Abstract Detail: Human
Drug Category: Marijuana/Cannabinoids
Topic: Epidemiology
Abstract Category: Original Research
Designation: M.S.

Abstract: Aim: The effects of cannabis use on the gastrointestinal tract (GIT) are not clear. Despite the well-established anti-emetic properties of cannabis, case reports of cannabinoid hyperemesis syndrome characterized by cyclic nausea and vomiting have increasingly appeared in the clinical literature. Population-based studies of cannabis gastrointestinal effects are scant. The aim of the current study is to estimate the association between cannabis use and GIT illnesses in a large sample of United States (US) adults recruited for the National Health and Nutrition Examination Survey (NHANES).
Methods: NHANES is designed to be nationally representative of the US non-institutionalized civilian population. The current study sample included adults (20-59 years) who were examined at NHANES Mobile Examination Center (MEC). Cannabis use questionnaire (self-administered) and current health status questionnaire (interviewer-administered) were conducted using Computer-Assisted Interview system. We defined recent cannabis use as using cannabis in the 30 days prior to NHANES examination. Similarly, recent GIT illness was defined as having a stomach or intestinal illness in the 30 days prior to NHANES examination. Logistic regression modelling was used to regress recent GIT illness on cannabis use status, adjusting for age, sex, tobacco smoking and other potential confounding variables.
Results: The total analytic sample was 19251 adults, of which 8950 never used cannabis; 7700 were former users; and 2601 were recent users. Compared to never users, recent cannabis use was associated with higher odds of recent GIT illness (OR= 1.4, 95% CI: 1.2, 1.7). Covariate adjustments did not change our conclusions; that is, cannabis use was associated with greater likelihood of GIT illness (OR= 1.3, 95% CI: 1.1, 1.6).
Conclusions: In a large nationally representative sample of US adults, we detected a positive association between recent cannabis use and GIT illness. Additional work exploring the possibility of reverse causation is warranted.

ASSOCIATION OF A PRODYNORPHIN GENETIC VARIANT WITH CANNABIS EXPOSURE IN HUMANS

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[1]The Rockefeller University

Abstract Detail: Human
Drug Category: Marijuana/Cannabinoids
Topic: Genetics
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: The prodynorphin gene (PDYN) encodes for the dynorphins, the main endogenous agonists for kappa-opioid receptors. Activation in the dynorphin/kappa system occurs due to exposure to specific drugs of abuse and stress. The aim of this study is to determine if two single nucleotide polymorphisms (SNPs) in PDYN, selected as markers for two previously reported haplotypes, are associated with cannabis use disorders. These two marker SNPs are: rs2281285 in intron 2, and rs2235749 in the 3' untranslated region of exon 4, which has been reported to be part of a functional haplotype that affects PDYN transcription.
Methods: The protocol was approved by the Institutional Review Board, and adult African American volunteers of either gender signed an informed consent. Volunteers (total n=555) were sequentially ascertained by a clinician, with the following phenotyping instruments: SCID-I interview for DSM-IV psychiatric diagnoses, and KMSK scales for dimensional measures of drug exposure. The PDYN SNPs rs2281285 and rs2235749 were genotyped with Illumina arrays.
Results: A contingency analysis revealed a significant association of the rs2281285 SNP with Cannabis Dependence diagnosis (Fisher's test $p<0.02$), and this finding survived adjustment for gender, in a multiple logistic regression. Cannabis KMSK scores (a dimensional measure of self-exposure) were also significantly greater in volunteers with the rs2281285 SNP than in those with the prototype (Mann-Whitney test, $p<0.014$). However, none of these associations were significant with the SNP from the other PDYN haplotype, rs2235749. The aforementioned p-values for SNP rs2281285 survived experiment-wise correction with the Bonferroni method.
Conclusions: This study suggests that genetic variation in specific regions of the prodynorphin gene is associated with greater self-exposure to cannabis in humans, and further implicates the dynorphin/kappa-receptor system in cannabis use disorders.

THE EFFECT OF VARENICLINE ON CANNABIS WITHDRAWAL FACTORS IN A PLACEBO-CONTROLLED PILOT TRIAL FOR CANNABIS USE DISORDER

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Abstract Detail: Human
Drug Category: Marijuana/Cannabinoids
Topic: Treatment
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: To determine the effect of varenicline on four factors of cannabis withdrawal.
Methods: In this 6-week pilot trial participants (N=72) were randomized to receive either varenicline (1mg bid; n=35) or matched placebo (n=37) as an adjunct to a brief motivational intervention. Primary outcomes for the current analysis included four factors of the Cannabis Withdrawal Scale previously identified in adults with cannabis use disorder: Negative Affect (NA), Autonomic, Somatic, and Craving. Factors were assessed at baseline and end-of-treatment (EOT) and compared within and between subjects using linear mixed effects modeling.
Results: Varenicline-treated participants reported a small yet significant reduction in NA from baseline to EOT ($p < .05$, $\Delta = 1.80$, $d = -0.31$), while placebo participants did not report a

significant reduction. Among participants who reported any NA at baseline (n = 51), this effect was strengthened ($p < .05$, $\Delta = 3.26$, $d = -0.51$). Participants receiving varenicline also reported significant reductions in Autonomic symptoms from baseline to EOT ($p < .05$, $\Delta = 1.33$, $d = -0.13$), while the placebo group did not. This effect did not change when including only those who reported any Autonomic symptoms at baseline. All participants reported significant reductions in Somatic and Craving factors across treatment conditions. Findings are considered preliminary as the study was not powered to test these effects.
Conclusions: While effect sizes were generally small, these results suggest that varenicline may target NA and autonomic symptoms in adults with cannabis use disorder. Fully powered testing of varenicline as a candidate for reducing NA and autonomic symptoms in adults with cannabis use disorder is warranted.

BASELINE PLASMA ENDOCANNABINOID LEVELS CORRESPOND TO THE ACUTE EFFECTS OF SMOKED CANNABIS IN NEAR-DAILY CANNABIS USERS

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Abstract Detail: Human
Drug Category: Marijuana/Cannabinoids
Topic: Neurobiology
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: The endocannabinoids (eCBs), anandamide (AEA) and 2-arachidonoylglycerol (2-AG), play an integral role in physiology, stress, mood, and behavior, yet the impact of cannabis use on eCBs is poorly understood. This study assessed plasma levels of eCBs and tetrahydrocannabinol (THC), ratings of cannabis intoxication ("high", "good drug effect") and cardiovascular endpoints before and after cannabis administration in cannabis smokers.
Methods: Twenty-six healthy, non-treatment-seeking, near-daily cannabis smokers were recruited. Participants smoked 75% of a NIDA cannabis cigarette (5.6% THC) using a cued paced-puffing procedure. Subjective-effects ratings, cardiovascular measures, and plasma samples of AEA, 2-AG, and THC were assessed at baseline and at eight timepoints beginning 15 min after cannabis administration.
Results: Cannabis significantly ($p<0.0001$) increased ratings of intoxication, heart rate and plasma THC levels. There was a significant positive correlation between baseline AEA levels and peak "high" ($r=.56$, $p=.004$) and "good drug effect" ($r=.50$, $p=.01$) following cannabis administration. Baseline 2-AG was negatively correlated with frequency of cannabis use (mean days/week; $r=-.56$, $p=.003$), and showed trending negative relationships with other measures of cannabis use (mean grams/day: $r=-.38$, $p=.059$; amount used in last week in grams/day: $r=-.34$, $p=.09$).
Conclusions: Baseline plasma eCB levels are associated with cannabis's acute subjective effects. Higher baseline AEA corresponded to greater "high" and "good effect" after smoking. More frequent cannabis use was associated with lower baseline 2-AG. Given that baseline eCB levels are lower in this population of cannabis users compared to published levels in non-

cannabis users, we hypothesize that baseline eCBs may be a biomarker of cannabis tolerance, i.e., heavier cannabis smokers have lower eCBs and are less sensitive to the intoxicating effects of cannabis. Future research will further explore how cannabis-induced changes in eCB levels impact physiology, stress, mood, and behavior.

EMERGING TRENDS IN MICRO-DOSING CANNABIS AMONG CANNABIS-USING YOUNG ADULTS IN LOS ANGELES

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Abstract Detail: Human
Drug Category: Marijuana/Cannabinoids
Topic: Behavior
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Since the legalization of recreational cannabis in CA, regulation has brought about standardized labeling of doses, creating an opportunity for modulation of intake – i.e., micro-dosing. There is limited understanding on current micro-dosing practices (i.e., reasons, methods), how it coincides with other emerging trends (i.e., CBD use), and how this affects subgroups (e.g., women) differently. This is particularly relevant for young adult users as they transition into adult roles and responsibilities.
Methods: In 2019, we surveyed 199 cannabis-using young adults (aged 23 to 31) in Los Angeles. We assessed whether participants micro-dosed by asking whether they "consumed small amounts of cannabis (e.g., 2.5mg)…" in last 12-months. Analyses examined micro-dosing practices, motivations, modes of administration, socio-demographic characteristics, and potential behavioral/mental health consequences (e.g., driving while under the influence, DSM-V), and gender differences.
Results: 41% of the sample micro-dosed in the past 12 months. The most popular reasons were to feel more relaxed (56%) and to relieve anxiety (38%). Other reasons included: to help focus (28%), sleep (27%), think creatively (27%), and for physical pain (25%). The most popular modes of administration were using a vaporizer for buds/flowers or oils (44%), pipe/bowl (38%), and edibles (24%). Micro-dosers tended to be older but there were no differences in cannabis use frequency (e.g., days of use, hits) or behavioral/mental health outcomes. Micro-dosers preferred CBD-dominant products relative to THC only/dominant products and were more likely to endorse using cannabis for medical than recreational purposes. For gender differences, we found that among micro-dosers, men scored higher on the DSM-V criteria for problematic use while women preferred using edibles.
Conclusions: While micro-dosers appear to lead mostly functional lives, continued monitoring of micro-dosing is needed to determine whether, or to what extent, micro-dosing might lead to more problematic levels of consumption, longer-term health impacts, and how consequences might diverge among subgroups.

CANNABIS USE 90 DAYS FOLLOWING CESSATION OF NABIXIMOLS FOR THE TREATMENT OF CANNABIS DEPENDENCE: FINDINGS FROM A PLACEBO-CONTROLLED RANDOMISED TRIAL

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Abstract Detail: Human
Drug Category: Marijuana/Cannabinoids
Topic: Treatment
Abstract Category: Original Research
Designation: M.D., Ph.D., Prof. Dr.

Abstract: Aim: Consistent with other substance use disorders, agonist medications have demonstrated some efficacy for CUD. There have, however, been few that have explored post-treatment outcomes. We examine cannabis use outcomes 12 weeks after cessation of treatment from a randomized placebo-controlled trial of nabiximols (an oro-mucosal spray containing approximately equal parts of THC and CBD extracted from cannabis plants) for the treatment of cannabis dependence.
Methods: A randomized, placebo-controlled trial with 128 participants who received either nabiximols (n=61) or placebo (n=67) for 12 weeks, in combination with psychosocial interventions. Self-reported number of days of cannabis use in the previous 28 days was measured at baseline, 4, 8, and 12 weeks (end of treatment) and again at 24 weeks (3 months after treatment ceased). Self-reported cannabis use data was validated with urinalysis at Week 24 interview.
Results: A factorial mixed effects regression model for repeated measures revealed that participants randomized to nabiximols used cannabis on 6.8 fewer days in the previous 28 days at week 12 (end of treatment) than the placebo group (p=0.002, CI: 2.1,11.4), and 6.7 fewer days in the previous 28 days at the week-24 follow-up than the placebo group (p=0.006, CI: 1.4,12.1). A significantly higher proportion of those in the nabiximols group (14/26; 54%) than the placebo group (6/29; 21%) reported abstinence from cannabis in the previous 28 days at the week-24 research interview OR=4.5, CI: 1.4, 16.2; p=0.014, NNT=3, CI: 2, 11).
Conclusions: The benefits of treatment incorporating nabiximols with psychosocial interventions in reducing cannabis use for those with CUD seeking treatment appear to persist for up to 3 months after the cessation of treatment. A large, multi-site trial appears to be appropriate to further assess the effectiveness of cannabinoid agonist treatment, most appropriate client characteristics, and best practice models of stepped care to adjunctive pharmacotherapy for CUD.

VARENICLINE IN THE TREATMENT OF CANNABIS USE DISORDER: IMPACT OF TOBACCO USE

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Abstract Detail: Human
Drug Category: Marijuana/Cannabinoids
Topic: Substance Use Disorder
Abstract Category: Original Research
Designation: B.A.

Abstract: Aim: To assess differential outcomes by tobacco use status in a placebo-controlled pilot trial of varenicline in the treatment for cannabis use disorder.
Methods: Participants (n=72) were randomized to receive either varenicline (goal dose 1 mg; n=13 smokers, 22 nonsmokers) or a placebo (n=19 smokers, 18 nonsmokers) to be taken twice daily over 6 weeks. Outcomes, including self-reported cannabis use (Timeline Follow-Back), negative affect as measured by withdrawal symptoms (Cannabis Withdrawal Scale; CWS), and cannabis craving (Marijuana Craving Questionnaire; MCQ) were collected at baseline and weekly thereafter. Primary outcomes were end of study treatment differences between varenicline and placebo stratified by cigarette smoking status.
Results: Although not powered to detect stratified differences, efficacy estimates are reported. No differences were observed between smokers and nonsmokers in baseline measures of cannabis use (Mean (SE) % using days = 96.7% (1.9) vs. 89.3% (4.1)), cannabis craving (48 (2.8) vs. 44.3 (2.5)) or negative affect (1.53 (0.31) vs. 1.30 (0.27)). However, smokers receiving varenicline reported fewer cannabis use days on average during treatment than those receiving placebo (42% (11.3) vs. 76.4% (8.5)) and nonsmokers in either condition (Varenicline: 52.9% (10) vs. Placebo: 53.6% (11.7)). Similarly, smokers receiving varenicline also reported a greater reductions from baseline in cannabis craving at end of treatment compared to the placebo (-28 (4.8) vs. -18.8 (4.8)) as well as nonsmokers regardless of randomization (Varenicline: -18.6 (4.4) vs. Placebo: -24.3 (5.2)). In contrast, nonsmokers receiving varenicline reported a greater reduction in negative affect from baseline compared to placebo (-1.04 (0.5) vs. -0.53 (0.61)) as well as smokers regardless of randomization (Varenicline: -0.66 (0.75) vs. Placebo: -0.50 (0.55)).
Conclusions: Preliminary results suggest varenicline may have differential effects in the treatment of cannabis use disorder as a function of tobacco use status.

CHANGING ATTITUDES TOWARD CANNABIS POLICIES IN AUSTRALIA – UNTANGLING THE EFFECTS OF AGE, PERIOD AND COHORT

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Abstract Detail: Human
Drug Category: Marijuana/Cannabinoids
Topic: Epidemiology
Abstract Category: Original Research
Designation: B.Sc.

Abstract: Aim: Australian support for cannabis legalization has been stasis for a decade since 2000s in the context of substantial international policy change. In 2016, key amendments were made to enable access to medicinal cannabis across Australia. The change in cannabis regulation has raised concerns about the relationship between policies, attitudes, and use. The

aim of this study is to examine trends of Australians' attitudes toward different cannabis policies and cannabis use.
Methods: Five waves of the National Drug Strategy Household Survey data between 2004 and 2016 were used, included 117,219 adult participants. Attitudes toward medical and recreational cannabis legalization, cannabis decriminalization and participants' intention to use cannabis were assessed, stratified by sex and personal history of cannabis use. Hierarchical age-period-cohort (HAPC) models estimated the role of age, period, and cohort on trends in attitudes toward different cannabis policies and cannabis use intention.
Results: There has been a surge in support for more liberal cannabis policies in 2016, after the level of support had remained stable for a decade. There was also a slight increase in cannabis use intention in the same year. The HAPC models confirmed that the shifted attitudes were principally attributable to period effects ($p<0.01$) rather than age effects ($p>0.05$). Birth cohort memberships were also influential, with people born between 1950 and 1969 more likely to support cannabis legalization and decriminalization ($p<0.01$). They were also more likely to use cannabis if cannabis became legally available. The results showed that age, period and cohort effects varied by sex and personal history of cannabis use.
Conclusions: Medical cannabis legalization in 2016 and cohort membership have independently contributed to support for more liberal cannabis policies and cannabis use intentions, suggesting that cohort-specific strategies may be needed to minimize any harm from the potential increase in cannabis use in Australia.

Choice/Demand/Reward

NEURAL MARKERS OF REWARD-SEEKING AND ATTITUDES TOWARD RISKY BEHAVIOR IN AFRICAN-AMERICAN YOUTH

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Abstract Detail: Human
Drug Category: Other, Alcohol and other drugs
Topic: Neurobiology
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Adolescence is a vulnerable period whereby youths' natural tendencies to explore and take risks leads to negative outcomes. As the striatum and prefrontal cortex (PFC) are involved in decision-making in the context of risks and rewards, we aimed to elucidate the fronto-striatal functional connectivity during a reward-seeking task in a sample of 11-to-14-year old participants.
Methods: Subjects were recruited as part of an ongoing randomized controlled trial aiming to prevent/delay risk-taking in African American youth. fMRI scans were acquired on a 3.0 Tesla scanner in 76 youths with no psychopathology (44 males; mean age=12.5 years). Reward-seeking was measured during the decision phase of a modified Wheel of Fortune (WOF) task, whereby participants were presented with probabilities of winning/losing points and asked to bet/pass on each trial. Participants completed a self-report measure indicating their level of agreement with peer experimentation with drugs and alcohol.

Results: Linear regression models indicated that risk-based attitudes predicted betting behavior, $F(1, 74)=5.67$, $p\leq.05$, $R2=.07$; youth who indicated acceptance of same-aged peers engaging in risky behavior (e.g. use cocaine and alcohol) bet more frequently across all WOF risk trials. Psychophysiological Interaction analyses revealed that high reward-seekers displayed less functional coupling between the striatum and ventrolateral PFC compared to low reward-seekers, $t(74)=2.56$, $p\leq.01$.
Conclusions: These results suggest that stronger coupling between the striatum (reward-seeking) and vlPFC (inhibitory control) may buffer adolescents' natural predisposition toward reward-seeking. Further, these younger participants' responses on attitudes toward peer risk-taking may be a proxy for their own future experimentation with drugs and alcohol, as they may not have engaged in risky behaviors yet. Eventually we will be able to assess whether the striatal-vlPFC functional connectivity measured at baseline will predict positive response to the intervention by delaying/averting risky behaviors.

CONVERGENT NETWORK-LEVEL BRAIN ALTERATIONS ACROSS DRUGS OF ABUSE: A META-ANALYSIS OF STRUCTURAL MRI STUDIES

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Abstract Detail: Human
Drug Category: Polydrug (i.e. Use of more than one drug combination)
Topic: Imaging
Abstract Category: Original Research
Designation: M.S.

Abstract: Aim: Neuroimaging studies have provided insight into the structural and functional brain alterations linked with substance abuse; yet, these studies often assess such alterations within the context of individual drugs (e.g., nicotine). Rather, neurobiological theories of addiction emphasize common network-level brain alterations across drug classes. Using emergent meta-analytic neuroimaging techniques, we sought to identify common structural brain alterations across drugs and to characterize the functionally connected networks with which such structurally-altered regions interact.
Methods: We performed a literature search and identified 87 studies characterizing gray matter volume (GMV) differences between substance users versus non-users. Using the Activation Likelihood Estimation (ALE) algorithm we identified convergent GMV reductions across all studies. Next, we characterized an "extended addiction network" (eAN) by identifying the brain areas that were functionally coupled with these structurally-altered regions. To do so, we performed resting-state functional connectivity (rsFC) and meta-analytic connectivity (maC) analyses using each structurally altered region as a seed and computed whole-brain functional connectivity profiles as the union of both rsFC and maC maps. We considered regions to constitute nodes in the eAN where at least 3 of the functional connectivity profiles overlapped. Finally, we performed hierarchical clustering with all of the eAN node's functional connectivity profiles to identify sub-networks linked with substance abuse.
Results: We identified the left insula, cingulate, and medial/superior frontal gyri as regions showing convergent GMV reductions among users. The overlap of these region's functional connectivity profiles identified the cingulate, bilateral insulae, putamen, and superior temporal

gyrus as regions of the eAN. Hierarchical clustering identified 3 sub-networks closely corresponding to the default-mode (posterior-cingulate, angular gyrus), salience (dorsal anterior cingulate, caudate), and executive control networks (lateral prefrontal and parietal cortex).
Conclusions: These outcomes indicate that structurally altered brain regions linked with substance abuse are functionally connected to canonical intrinsic connectivity networks (default-mode, salience, and executive control).

FAMILY HISTORY OF ALCOHOL USE PROBLEMS IS ASSOCIATED WITH ENTORHINAL REWARD ACTIVATION IN THE ABCD STUDY

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Abstract Detail: Human
Drug Category: Alcohol
Topic: Imaging
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Individuals whose parents have experienced problems with alcohol are more likely to develop problems themselves. Reward system functioning has been identified as an important target in the study of this risk. Here we utilize a large, multi-site imaging dataset of 9 and 10-year-olds to investigate whether children with a family history of alcohol use problems (FH+) demonstrate different reward-system activation than family history negative (FH-) children. We also test whether reward-system activation is associated with experimentation with alcohol.
Methods: Participants were from the Adolescent Brain Cognitive Development (ABCD) Study Release 2.0 (baseline data; N=7,164). 14.9% were FH+. We used a monetary incentive delay task to measure brain functioning during reward anticipation and feedback. We used the following variables to test the association between family history of alcohol use problems and reward system functioning: FH+/- as the predictor of interest; 22 reward-related regions of interest as dependent variables; site and family as random effects; and sex, race/ethnicity, household income, and subject motion as fixed-effect covariates. We also used the presence/absence of sipping alcohol that occurred not as part of a religious ceremony (17.0% reported non-religious sipping).
Results: Family history was not significantly associated with left or right nucleus accumbens activation during reward anticipation or feedback. There was, however, an association between family history and activation in the right entorhinal cortex during reward anticipation (FH+ > FH-; p=.002). Non-religious sipping was not associated with reward-system activation.
Conclusions: In this large, nationally representative dataset, family history of alcohol use problems was significantly associated with right entorhinal cortex activation. The entorhinal cortex is part of the limbic system and has projections to the ventral striatum; as such it has been identified as part of the circuitry that contributes to addictive behavior. Longitudinal data from ABCD will allow for the mapping of this association over time.

SEX DIFFERENCES AND THE IMPACT OF ALTERNATIVE REINFORCERS IN OXYCODONE SELF-ADMINISTRATION IN SQUIRREL MONKEYS

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Abstract Detail: Animal Study
Drug Category: Opiates/Opioids
Topic: Sex Differences
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Preclinical studies have previously shown that females self-administer oxycodone more than males. The extent to which the availability of alternative reinforcers that vary in magnitude will differentially impact preference for, and intake of, oxycodone between males and females has yet to be established. It was hypothesized that differences in oxycodone preference as a function of alternative reinforcer magnitude between males and females will be a reflection of the disparity in oxycodone intake.
Methods: Squirrel monkeys (n=8; 4 males, 4 females) responded under concurrent second-order FR3(FR5:S);TO45s schedules of reinforcement for intravenous oxycodone (0.001-0.1 mg/kg) on one lever and sweetened condensed milk (10, 20, 30% v/v in water) or water on another. The linear portion of the dose-response functions for percent injection-lever (%ILR) were fitted to straight lines and analyzed with a linear interpolation to generate ED50 values. Potency ratios were determined from the ED50 values using the following formula: ED50 of the least potent curve/ED50 of the most potent curve.
Results: At all milk concentrations, self-administration of oxycodone in males and females engendered a prototypical inverted U-shaped curve; however, the peak self-administered oxycodone dose was up to 100-fold more potent in females than in males. Furthermore, females responded up to 3x more for oxycodone than males. Varying the magnitude of the alternative reinforcer (e.g., increasing the milk concentration), decreased the potency of oxycodone preference by less than 2-fold in males. In females, preference for oxycodone was approximately 5- and 10-fold more potent when 10% milk was available compared to 20% or 30% milk, respectively.
Conclusions: These results expand on previous reports showing that oxycodone is self-administered more in females. Further, females appear to be more sensitive to the reinforcing effects of oxycodone and the magnitude of the alternative reinforcer influences the reinforcing potency of oxycodone in females, but not males.

UNCERTAINTY AS A FACTOR CONTRIBUTING TO DRUG VS. NONDRUG CHOICE

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Abstract Detail: Animal Study
Drug Category: Stimulants
Topic: Behavior

Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Relative to non-drug reinforcers, illicit drugs may be more uncertain or unpredictable in terms of their availability, quality, and time and effort to obtain, and this may be an important component of drug taking at the expense of engaging in nondrug-related activities. We have shown that variable schedules and magnitudes of cocaine are generally chosen over fixed ones in drug vs. drug choice. In drug vs. nondrug choice, we predict that cocaine choice will be more extreme when available under variable-cost conditions. Conversely, we predict that food will more effectively compete with cocaine when food availability is variable.
Methods: Adult male (N=2) and female (N=2) rhesus monkeys chose between cocaine (0.01-0.1 mg/kg/injection) and food (4 pellets/delivery). In control conditions, both schedules were fixed and predictable. In variable-cocaine or variable-food conditions, the response requirement was variable on the cocaine or food lever, respectively, while the requirement on the other lever remained fixed.
Results: At sufficiently large response requirements, cocaine choice was greater under a variable requirement than under a fixed requirement, resulting in leftward shifts in the cocaine dose-response function. With food, results were more variable at the individual-subject level. As predicted, however, average cocaine choice was reduced when food was available under a variable requirement, and the average cocaine dose-response function was shifted rightward. We are currently adding subjects to allow detection of potential sex differences.
Conclusions: Our findings suggest that variable availability could contribute to excessive allocation of behavior toward procuring illicit drugs at the expense of more predictable, nondrug alternatives. Results with food suggest that a non-drug reinforcer may more effectively compete with drug reinforcement when its delivery is made variable. This could have implications for treatments like contingency management that arrange nondrug reinforcement contingent on drug free urine samples.

IMPACT OF OPIOID DEPENDENCE AND WITHDRAWAL ON THE RELATIVE REINFORCING EFFECTS OF FENTANYL, METHAMPHETAMINE, AND COCAINE IN RATS

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Abstract Detail: Animal Study
Drug Category: Opiates/Opioids
Topic: Tolerance/Dependence
Abstract Category: Original Research
Designation: M.S.

Abstract: Aim: The co-injection of cocaine and heroin has been common for decades; however, recent estimates suggest increased popularity of stimulant-opioid mixtures, with over 50% of treatment-seeking opioid users reporting regular stimulant use. The goal of the current study was to determine how opioid dependence and withdrawal affect the reinforcing effects of fentanyl, cocaine, and methamphetamine.

Methods: Male Sprague Dawley rats were trained to self-administer fentanyl under a progressive ratio (PR) schedule of reinforcement. PR dose-response curves for fentanyl, methamphetamine, and cocaine were generated. Dependence was then established by administering escalating doses of morphine (10-40 mg/kg) twice-daily for four days and maintained by once-daily injections of 40 mg/kg morphine. To evaluate the impact of opioid dependence and withdrawal on the self-administration of fentanyl (0.032-32 ug/kg/inf), cocaine (0.32 mg/kg/inf), and methamphetamine (0.1 mg/kg/inf), sessions occurred either 12- or 20hrs after the morphine, respectively. Withdrawal signs were assessed prior to self-administration sessions.
Results: Fentanyl, cocaine, and methamphetamine all functioned as reinforcers. After establishing opioid dependence, rats exhibited withdrawal signs by 20hrs, but not 12hrs, after their last dose of morphine. During opioid-withdrawal, the fentanyl dose-response curve was shifted upward whereas it was shifted downward and to the right when evaluated in rats currently dependent on opioids. The reinforcing effects of cocaine and methamphetamine were unchanged by either condition.
Conclusions: The current studies provide direct evidence that the reinforcing effects of fentanyl are increased in opioid-withdrawn rats and suppressed in rats that are dependent on opioids relative to rats that are not physically dependent on opioids. Opioid dependence and withdrawal did not affect the reinforcing effectiveness of methamphetamine or cocaine. These findings suggest that motivations to use opioids are dependent on the state of the individual whereas stimulants retain their reinforcing effects regardless of whether the individual is in a state of opioid dependence or withdrawal.

BASELINE ALCOHOL USE AS MODERATOR OF TREATMENT OUTCOME IN OPIOID USE DISORDER: LEVERAGING A HARMONIZED DATA SET OF TWO LARGE CLINICAL TRIALS

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Treatment
Abstract Category: Original Research
Designation: M.D., Ph.D.

Abstract: Aim: Comorbid opioid use disorder (OUD) and heavy alcohol use is common. Several studies reported an initial decrease in alcohol use in response to treatment with medications for opioid use disorder (MOUDs). However, few studies exist that explored alcohol use itself a predictor of the outcome for adherence to MOUDs. We hypothesize that an increase in the number of heavy drinking days (HDD) correlates with poor treatment response to MOUDs. We additionally hypothesize that this effect is dependent on which MOUD is received, as naltrexone has indications for use in reducing heavy drinking.
Methods: Combining and harmonizing two, large, randomized clinical trials from the National Drug Abuse Treatment Clinical Trials Network (CTN) (CTN0027 and CTN0051, N=1,839), we tested 3 predictors in the 30 days prior to screening using logistic regression: 1) total number of drinks, 2) number of heavy drinking days, 3) decrease in alcohol use, correlating them to

relapse at the end of the study defined as 4 consecutive weeks of opioid use either on self-report and urine toxicology, or 7 consecutive days of self-reported opioid use. The primary outcome for the two studies was adherence to a MOUD at 24 weeks of treatment.
Results: We detected a significant treatment effect, better from the inpatient buprenorphine group (CTN0051), when compared to the outpatient methadone (CTN0027) (OR = 1.80, p=0.01), outpatient buprenorphine (CTN0027) (OR = 2.31, p<.001), and inpatient extended-release naltrexone (1.53, p=0.02) groups. We also detected an interaction in those patients who had a large baseline alcohol use had better outcome, but only for the outpatient buprenorphine group (OR=1.85 for each additional 0.5 drinks/day, p=0.03), and inpatient extended-release naltrexone group (OR=1.23, p=0.04). We did not detect significant effects for other moderators.
Conclusions: The total number of drinks may be a more informative predictor variable than heavy drinking days, especially in outpatient treatment.

Cognition Behavior

DOSE-SPECIFIC EFFECTS OF PREGNENOLONE ON RESPONSE INHIBITION IN INDIVIDUALS WITH ALCOHOL AND COCAINE USE DISORDER

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Abstract Detail: Human
Drug Category: Alcohol
Topic: Substance Use Disorder
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Chronic substance use related adaptations have been shown to down-regulate GABAergic transmission (Biggio et al., 2007) and levels of neuroactive steroids (Purdy et al., 1991), which are potent modulators of the GABAA receptor. Cognitive deficits, such as impaired response inhibition and impulse control, have been observed in individuals with substance use disorders (SUDs), and may play an important role in the progression, maintenance and risk for relapse (Beatty et al., 1995; Aharonovich et al., 2003, 2006). Therefore, interventions that improve cognition may prove clinically relevant in the larger treatment of SUDs. Here we tested the effects of two doses of the neuroactive steroid precursor pregnenolone (PREG) vs. placebo (PLA) on response inhibition in treatment seeking individuals with alcohol and cocaine use disorder (AUD and CUD).
Methods: Eighteen treatment seeking individuals with AUD and CUD received PREG (300mg; 500mg/day) vs. PLA for 8 weeks. In week 1 (Session 1) and week 8 (Session 2) participants completed a computer version of the Stop Signal Task (SST). Linear Mixed Effect models assessed differences in SST performance as a function of session and medication group.
Results: Individuals receiving 300mg PREG had higher correct reaction times (RT) on GO trials compared to individuals receiving 500mg PREG or PLA, potentially implying more cautious accuracy processing. Moreover, the 300mg PREG group had significantly fewer direction errors than the 500mg PREG or PLA groups. Lastly, the 300mg PREG group had significantly higher stop signal delay (SSD) compared to the 500mg PREG and PLA groups,

indicating higher proportion of successful inhibition in response to a stop signal during the task. The only effect of session was lower SSD in Session 2 compared to Session 1 across all three groups.
Conclusions: Findings highlight dose-specific improvements in response inhibition/impulse control in SUD individuals receiving PREG treatment.

THE IMPACT OF SUBSTANCE ABUSE ON BRAIN ACTIVITY DURING RISKY-DECISION MAKING: A NEUROIMAGING META-ANALYSIS

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Abstract Detail: Human
Drug Category: Polydrug (i.e. Use of more than one drug combination)
Topic: Imaging
Abstract Category: Original Research
Designation: M.Sc.

Abstract: Aim: Elevated risky decision-making (risky-DM) is a common behavioral phenotype linked with substance use disorders. Multiple neuroimaging studies have characterized differential brain activity among substance users (vs. non-users) during risky-DM. However, such findings have been, to some degree, inconsistent potentially due to differences across studies regarding the paradigms utilized, variation in the type of drugs considered, and/or participants' drug use patterns. We utilized meta-analytic techniques allowing for the integration of neuroimaging results to: (1) elucidate convergent brain activity associated with risky-DM separately among substance using and non-using participants, (2) examine activity convergence related to risky-DM among both groups, and (3) characterize differential activity convergence between substance users and non-users.
Methods: We performed a permutation-based meta-analysis utilizing risky-DM related contrasts from substance using (25 contrasts, 14 studies) and non-using participants (40 contrasts, 29 studies). This technique randomly sub-sampled the larger dataset to equal the number of contrasts in the smaller dataset, calculated thresholded Activation Likelihood Estimation (ALE) images separately for both datasets, and performed contrast (i.e., substance users vs. non-using participants) and conjunction analyses between now equally sized groups. These steps were repeated 500 times and each voxel's frequency of reaching significance was recorded.
Results: When considering non-using participants, we observed convergent activity in brain regions involved in reward processing, inhibitory control, and linked with the default mode network (i.e., anterior cingulate cortex (ACC), caudate, insula, and precuneus). When considering substance using participants, we observed convergent activity in salience-related regions (i.e., ACC, insula). The ACC was identified as a common risky-DM related region among both groups. Critically, substance users showed reduced convergent activity in reward-related brain regions (i.e., ACC, caudate, and thalamus) as compared to non-using participants.
Conclusions: Our findings support the systems-level perspective that substance abuse is linked with reduced activity in reward-related regions, a mechanism that may contribute to maladaptive decision-making under risk.

ABNORMALITIES IN RICH-CLUB ORGANIZATION OF THE STRUCTURAL BRAIN CONNECTOME IN COCAINE USE DISORDER

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Abstract Detail: Human
Drug Category: Stimulants
Topic: Imaging
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Chronic cocaine use is associated with cognitive deficits. Neuroimaging studies have revealed localized effects of cocaine on brain structure, including reduced gray matter volume and white matter integrity in frontal regions. However, it is unclear how cocaine may affect the structural organization of the brain and its relationship to cognitive performance.
Methods: The sample included 37 adults with cocaine use disorder (CUD) and 38 age-, gender-, and race-matched controls. Participants completed comprehensive neuropsychological testing and diffusion-weighted imaging on a 3T scanner. Connectome matrices based on fractional anisotropy (FA) were built using brainGraph. The HCP Multi-Modal Parcellation and Harvard-Oxford atlases were used to define 360 cortical and 14 subcortical nodes, respectively. The rich club was defined as the 9% of nodes with the highest degree. Mean FA within the rich-club network was compared between groups and correlated with global cognitive functioning. Groups were also compared on modularity and transitivity (measures of network segregation) and small-worldness (a measure of network organizational efficiency).
Results: The sample was predominantly male (60%) and African American (77%), with a mean age of 44.31 years. On average, participants with CUD had used cocaine regularly for 17.68 years and on 10.35 of the past 30 days. Participants with CUD had lower global cognitive functioning scores compared to controls (M=44.75 vs. 49.11; p=.001). There were no group differences on modularity, transitivity, or small-worldness, but participants with CUD had lower FA connection strength within the rich-club network compared to controls ($p<.05$). Among CUD, lower connectivity within the rich-club network correlated with poorer cognitive function (rpartial=.390, $p<.05$).
Conclusions: Our results suggest that CUD is associated with abnormal rich-club organization, and that the impaired connectivity in this rich club may explain some of the cognitive deficits seen in persons with CUD.

DOPAMINE D2/D3 RECEPTOR ASSOCIATIONS WITH STROOP PERFORMANCE AND DEFAULT-MODE NETWORK SUPPRESSION IN COCAINE USE DISORDER

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Abstract Detail: Human
Drug Category: Stimulants

Topic: Imaging
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Stimulant addictions are associated with lower availability of dopamine type-2 receptors (D2R) and greater availability type-3 receptors (D3R). Links between lower D2R levels, impaired cognitive performance, and deficient suppression of the default-mode network have been observed in healthy and addicted populations; however, there is limited evidence regarding a potential role of elevated D3R in influencing cognitive control processes.
Methods: Sixteen individuals with a cocaine use disorder (CUD) and 16 matched healthy comparison participants completed [11C]-(+)-PHNO PET imaging to assess availability of D2R/D3R and a Stroop task during fMRI to assess default-mode network suppression during cognitive control. Stroop performance was assessed prior to and immediately following multiple in-scanner runs and tested for relationships with binding in the D2R-rich dorsal putamen and D3R-rich substantia nigra. Default-mode network suppression was also examined for relationships with Stroop performance and D2R- and D3R-related binding.
Results: Consistent with prior reports using [11C]-(+)-PHNO to assess dopamine receptors in similarly sized samples of stimulant users, CUD individuals had greater binding (BPND) in the D3R-rich substantia nigra ($t30=2.13$, $p=0.042$) and lower BPND in the D2R-rich dorsal putamen did not reach significance ($t30=1.85$, $p=0.074$). On average, there were no differences in Stroop performance or default-mode suppression between groups. In HC individuals, lower D2R-related binding was associated with shorter interference delays ($F1,13=11.97$, $p=0.004$) and greater suppression of the default-mode network ($F1,13=4.48$, $p=0.054$). By comparison, in CUD, greater D3R-related binding was associated with shorter interference delays ($F1,13=7.99$, $p=0.014$) and greater default-mode network suppression ($F1,13=13.01$, $p=0.003$).
Conclusions: To our knowledge, this is the first report linking elevated D3R-related receptor availability in CUD to improved neurocognitive performance. These results provide some insight into the heterogenous neurocognitive profiles of individuals with a stimulant addiction and warrants further research into the potential role of elevated D3R in additional cognitive domains implicated in addictions.

COMBINING DOPAMINE AGENTS TO ENHANCE COGNITION AND REDUCE COCAINE USE: A RANDOMIZED CLINICAL TRIAL OF LEVODOPA AND ROPINIROLE

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Abstract Detail: Human
Drug Category: Stimulants
Topic: Treatment
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Cocaine use disorder (CUD) has been linked to deficits in CNS dopamine (DA) availability and transmission. Chronic cocaine users show impairments in cognitive

processes associated with DA. Medications aimed at bolstering cognitive functions via DA modulation might enhance treatment outcome. We tested this hypothesis by simultaneously enhancing pre-synaptic DA release (with levodopa) and post-synaptic DA receptor function (with the D2 agonist, ropinirole). We predicted that the DA medication combination would be associated with reduced cocaine use, and this treatment effect would be mediated by improvement in cognitive function.
Methods: The trial used a double-blind, parallel-group design with four treatment arms comparing placebo (PLC) to L-DOPA alone (LR0), L-DOPA plus ropinirole 2mg/d (LR2), and L-DOPA plus ropinirole 4 mg/d (LR4). Adults (n=110) with CUD attended thrice weekly clinic visits for 10 weeks. Medication dose escalation (weeks 1-3) was followed by maintenance (weeks 4-10). Potential mediators, assessed at week 5 while controlling for baseline and week 3, consisted of behavioral lab measures of attention, working memory, impulsivity, and decision-making. The primary outcome measure was Treatment Effectiveness Score (TES), defined as the number of cocaine-negative urines collected from weeks 5-10.
Results: Bayesian mediation examined indirect and total effects of the relationships between each active treatment (compared to PLC) and TES. Total effects were supported for LR0 (PP=91.2%) and LR2 (PP=86.6%), but less so for LR4 (PP=64.9%). Indirect effects demonstrated that 22.3% and 35.4% of the total effects of LR0 and LR2 on TES were mediated by changes in impulsivity from baseline to week 5.
Conclusions: L-DOPA alone and combined with ropinirole resulted in decreased cocaine use relative to placebo, and this effect was partly mediated by change in impulsivity. The mediation effect was strongest for L-DOPA plus low dose ropinirole (PP=90.7%). These preliminary findings offer a plausible mechanism by which DA-enhancing agents transmit change in cocaine use.

Craving

SYMPTOMATOLOGY AFFECTS SKIN CONDUCTANCE RESPONSE TO PATIENT AND IMPATIENT DECISIONS IN TREATMENT-SEEKING OPIOID USERS

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Neurobiology
Abstract Category: Original Research
Designation: B.Sc.

Abstract: Aim: Impulsive decision-making characteristic of addictive disorders has been shown to be strongly context dependent. We hypothesized that clinical states lead to contextual changes in impulsive choice that precipitate relapse. Inconsistent findings on the relation

between self-reported symptoms and relapse suggest that measuring psychophysiological manifestations of these symptoms may add much needed precision to their evaluation. We addressed these questions in a group of opioid users receiving outpatient methadone maintenance treatment. We explored how craving, withdrawal symptoms, anxiety, and skin conductance (index of physiological arousal) were related to impulsive behavior in a delay discounting task.
Methods: 38 individuals with Opioid Use Disorder (OUD) who endorsed persistent craving participated in 2 sessions - one before the participant received methadone and one after (order randomized). On each session, we employed validated instruments to assess self-reported craving, withdrawal, and anxiety. Participants then completed a delay discounting task while skin conductance response (SCR) was measured.
Results: SCR was significantly greater during trials in which subjects made a less as compared to a more impulsive choice in post-methadone ($n=17$, $p<0.05$) but not pre-methadone sessions. In post-methadone sessions only, anxiety modulated SCR by increasing it during more impulsive choices and decreasing it during less impulsive choices ($n=17$, $p<0.05$). Craving relationship to SCR was differential depending on choice: intensity and episode length were negatively correlated with SCR during impulsive choices (Spearman rho=-0.626 and -0.661 respectively, $p<0.05$, $n=15$) but positively correlated with SCR during patient choices (Spearman rho=0.777 and 0.759 respectively, $p<0.05$, $n=15$). Overall, more impulsive individuals showed lower SCR during patient choices (Spearman rho=-0.719, $p<0.05$, $n=17$).
Conclusions: Symptomatology interacts with the relationship between impulsive choice and physiological arousal in individuals with OUD. Craving and anxiety invert the arousal response to patient choices. Further elucidation of the physiological relationship between craving, anxiety and decision-making could help understand, predict, and prevent relapse in OUD.

HOW DO STRESS AND CRAVING LEAD TO RELAPSE IN OPIOID USE DISORDER? DETERMINING SENSITIZATION EFFECTS IN THE LOCUS COERULEUS NOREPINEPHRINE SYSTEM IN HUMANS

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Imaging
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Fluctuating craving and stress contribute to opioid use disorder (OUD) treatment failure. However, we lack a complete understanding of these factors, particularly at the neural systems-level. Preclinical studies suggest the locus coeruleus norepinephrine (LC-NE) system is a candidate pathway through which stress and craving promote opioid reuse. This system can be reliably imaged in humans using high-resolution neuromelanin-sensitive MRI, a noninvasive proxy measure of long-term LC-NE function and integrity. Inter-individual differences in this measure may be indicative of a more sensitized LC which can contribute to

stress and craving, leading to opioid reuse. Thus, here we aimed to 1) examine stress, craving, and opioid use patterns studied serially and longitudinally in OUD, and 2) test for moderation by inter-individual differences in LC-NE neuromelanin.
Methods: 37 OUD participants were followed for 8 weeks during buprenorphine-assisted outpatient treatment (272 total sessions), during which weekly measures of ongoing stress exposure, craving and opioid use were collected. A subset (n=17) also completed one neuromelanin-sensitive MRI scan. Time-lagged linear mixed models were used to examine patterns of stress, craving and use over time.
Results: Stress exposure (df=230, p=0.04) and craving (df=230, p=0.006) predicted session-to-session opioid use. However, the relationship between stress and prospective use was reduced with craving in the model (p=0.59), suggesting it was fully explained by stress-related increases in craving (df=264, p=0.047). Participants with higher LC-NE neuromelanin experienced disproportionately increased craving in the context of stress exposure (df=116, p=0.018, interaction effect controlling for age), in support of "sensitization-like" effects in LC-NE moderating these clinically relevant outcomes. Years of opioid use were associated with higher LC-NE neuromelanin (df=123, p=0.0003, controlling for age), further supporting opioid-specific LC-NE dysregulation.
Conclusions: Craving and stress proximally predict relapse behavior in OUD that impedes treatment success. LC-NE neuromelanin presents a novel, highly translational neural systems-level marker that links stress, craving and opioid reuse.

DEVELOPING A TAXONOMY OF HEROIN CRAVING IN OUTPATIENTS BEING TREATED FOR OPIOID-USE DISORDER

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Substance Use Disorder
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Craving is considered a core symptom of opioid-use disorder (OUD) but has not been reliable as a predictor of treatment success or drug use during treatment. Our group has found that associations among craving, stress, and lapse may vary across patients. In the analyses presented here, we examined whether we could identify groups of patients with distinct trajectories of craving during the early months of treatment, and whether those groups differed in their propensity to lapse and/or likelihood of dropout.
Methods: For 16 weeks, outpatients (n = 237) with OUD reported on their heroin craving severity at three random times during their day using smartphone-based ecological momentary assessment (EMA). Participants also initiated EMA entries when they used drugs. Growth mixture models were fit to the EMA craving data to identify subgroups.
Results: Model fit indices supported a four-trajectory solution. Trajectory 1 (n = 22) was characterized by initially low heroin craving that increased to a peak near the middle of treatment, then decreased. Trajectory 2 (n = 20) was characterized by initially high heroin craving that decreased during treatment. Trajectory 3 (n = 169) was characterized by

consistently low levels of heroin craving. Trajectory 4 (n = 26) was characterized by initially high levels of heroin craving that continually increased over time.
The four trajectory groups displayed markedly different patterns of drug use during treatment. The "high and increasing craving" group reported the highest frequencies of heroin and other drug use during treatment; the "low craving" group reported the lowest frequencies of use and was also the least likely to drop out of treatment.

Conclusions: Differences in dynamic patterns of change in opioid craving during agonist-maintenance treatment relate to propensity to lapse and dropout. We are currently examining how to identify group membership as soon as patients enter treatment.

Lifecourse

REINFORCEMENT LEARNING IN AGING COCAINE SMOKERS

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Abstract Detail: Human
Drug Category: Stimulants
Topic: Behavior
Abstract Category: Original Research
Designation: M.A.

Abstract: Aim: Cocaine smokers in the US are aging, yet little is known about the functional status of this group as they age. Previous research indicates that cocaine users have atypical learning from behavioral reinforcers relative to controls; this domain has not yet been studied in aging cocaine users. Reinforcement learning is a key capacity sub serving adaptive goal-directed behavior. Here, we assessed reinforcement learning in aging (50-60 years old) cocaine smokers relative to controls. To better match groups, controls were allowed to report cannabis, tobacco, and alcohol use.
Methods: 21 non-treatment-seeking older cocaine smokers (≥2x/week; ≥15 years of weekly cocaine use) and 19 controls completed a probabilistic reinforcement learning task, under gain and loss monetary conditions with reversal learning (i.e. probabilistic contingencies switched). Outcomes included response latency and optimal choice. Learning was assessed using a 2-stage Q model which assessed learning as a function of feedback and reinforcement type.
Results: Cocaine smokers (52.8±2.6 years old, 4F; cocaine use: 4.0±1.4 days/week) and controls (52.7±2.6, 4F) were well-matched demographically, but cocaine users reported somewhat higher cannabis, alcohol and cigarettes use than controls. Cocaine smokers exhibited slower overall learning rate than controls ($p<.01$), regardless of learning stage (feedback/reward) or condition (gain/loss). In cocaine users, years of ≥weekly cocaine use was negatively correlated with rates of learning from feedback under monetary gain ($r=-.45$, $p=.04$).
Conclusions: Data suggest that, when tested under controlled conditions, aging cocaine smokers exhibit lowered reinforcement learning relative to controls. Further investigations to examine the mechanisms of findings and functional implications are warranted.

AGE DISPARITIES IN SIX-MONTH TREATMENT RETENTION FOR OPIOID USE DISORDER

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Treatment
Abstract Category: Original Research
Designation: M.D.

Abstract: Aim: It is unknown if adolescents are retained in opioid use disorder (OUD) treatment at similar rates as adults, or if pharmacologic treatment affects the association between age and retention. We examined the association between age and six-month OUD treatment retention, and whether any such association was moderated by medication treatment.
Methods: In this retrospective cohort study, we used a large insurance database with OUD treatment claims from 2006-2016. We analyzed 261,356 OUD treatment episodes in 3 age groups: adolescent (ages 12-17, n=4,979), young adults (ages 12-17, n=76,229) and older adults (ages 25-64, n=180,148). We used logistic regression to estimate prevalence of six-month treatment retention while adjusting for covariates.
Results: Prior to adjusting for treatment type, there was an association between age and retention such that adolescents were less likely to be retained than adults: Retention prevalence for adolescents was 17.6% (95% CI 16.5-18.7%) compared to 25.1% (95% CI 24.7-25.4%) for young adults and 33.3% (95% CI 33.0-33.5%) for older adults. After stratifying by treatment type, the association between age and retention was markedly reduced. For example, for persons who received buprenorphine, adjusted six-month retention improved to 40.4% (95% CI 36.9-44.0%) for adolescents, compared to 39.9% (95% CI 39.4-40.4%) for young adults and 49.4% (95% CI 49.1-49.8%) for older adults. Within each age group, buprenorphine was more strongly associated with retention than naltrexone or psychosocial services only. Persons with commercial insurance were more likely to receive medication treatment than those with Medicaid (73% vs 36%; $\chi 2=57{,}870.6$, $p<.001$).
Conclusions: Age disparities in six-month OUD treatment retention are strongly related to age disparities in receipt of medication treatment. Buprenorphine appears to be more effective than naltrexone or psychosocial services alone for adolescents with OUD. Results point to need for improved implementation of evidence-based medication treatment for all persons with OUD, regardless of age or insurance status.

EFFECT OF IN UTERO SUBSTANCE USE EXPOSURE, BIRTHWEIGHT AND ETHNICITY ON CHILDHOOD GROWTH FROM BIRTH THROUGH 16 YEARS

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Abstract Detail: Human
Drug Category: Polydrug (i.e. Use of more than one drug combination)

Topic: Epidemiology
Abstract Category: Original Research
Designation: B.A., M.P.H.

Abstract: Aim: The long-term effects of in utero/prenatal substance use exposure on human physical health are largely unknown. There are no previous studies reporting growth trajectories beyond age 9 by prenatal substance use exposure among ethnically diverse study samples. This study reported the effects of prenatal substance use on pediatric body mass index (BMI) growth curves through age 16 among children primarily prenatally exposed to cocaine (PCE) controlling for other substances (tobacco, cannabis, alcohol).
Methods: A total of 13,819 growth data points from the Maternal Lifestyle Study (N = 1,388, 66% non-Hispanic black, 10% mixed race, 48% female) were analyzed. Generalized estimating equation models compared BMI growth curves by PCE (vs. no exposure), low birthweight (LBW), and race/ethnicity while controlling for age and other substance use.
Results: No statistically significant differences were found in BMI %ile growth curves from age 2-to-16 in PCE versus non-PCE children. Children born low birthweight (<2500g) had significantly lower BMI %iles versus those born LBW (56.6% versus 66.6%, $p<0.001$) at age 16. Asians had significantly lower BMI %iles versus all other ethnic groups at age 16 (13% versus 55-67% for all other groups, $p<.01$ for all comparisons).
Conclusions: This is the first study to compare longitudinal growth from birth to age 16 among PCE versus non-PCE children from ethnically diverse backgrounds. While the data is preliminary, results provide early insight into how prenatal substance use exposure, LBW and ethnicity may impact growth throughout childhood.

Nicotine/Tobacco

EFFECTS OF SMOKING STATUS AND STATE ON INTRINSIC CONNECTIVITY

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Abstract Detail: Human
Drug Category: Nicotine/Tobacco
Topic: Neurobiology
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Smoking behavior during the first 24 hours of a quit attempt is a significant predictor of long-term abstinence, yet little is known about the neurobiology of early tobacco abstinence. Specifically, the effects of acute tobacco deprivation and reinstatement on human brain function—particularly at the level of large-scale network dynamics—remain incompletely understood. To address this gap, this study used a mixed within- and between-subjects design to assess the effects of smoking status (yes/no smoker) and state (deprived versus satiated) on whole-brain patterns of intrinsic connectivity.
Methods: Forty-two tobacco smokers participated in resting state fMRI following overnight abstinence (deprived state) and again following smoking reinstatement (satiated state). Sixty

healthy control non-smokers participated in a single resting state scan using the same acquisition parameters. Functional connectivity data were analyzed using both a canonical network-of-interest (NOI) approach and a novel, whole-brain, data driven approach, intrinsic connectivity distribution (ICD).
Results: NOI-based analyses indicated decreased functional connectivity within frontoparietal and salience networks among smokers relative to nonsmokers, as well as effects of smoking state on default mode connectivity. In addition, ICD analyses identified novel between-group differences in subcortical-cerebellar and cortico-cerebellar networks that were largely smoking state dependent.
Conclusions: These data demonstrate the importance of considering smoking state and the utility of using both theory- and data-driven analysis approaches. In addition, given the prognostic significance of smoking within the first 24 hours of a quit attempt, these data provide much needed insight into the functional neurobiology of early abstinence beyond previously studied networks and may be used in the development of novel treatments.

ORGANIZATIONAL CHANGE SUPPORTS CULTURE CHANGE AND BETTER TREATMENT OUTCOMES FOR TOBACCO USE DISORDERS IN OUTPATIENT BEHAVIORAL HEALTH TREATMENT AGENCIES

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Abstract Detail: Human
rug Category: Nicotine/Tobacco
Topic: Treatment
Abstract Category: Original Research
Designation: M.D., M.P.H.

Abstract: Aim: Tobacco use disorders (TUD) are very common among individuals treated in mental health and addiction treatment agencies, resulting in serious health disparities and shortened life span. The treatment culture in these agencies has not addressed tobacco resulting in limited assessment, treatment, or referral for TUD. Effective ways to change this culture are needed.
Methods: This NCI-funded R01 cluster-randomized clinical study compared 7 agencies receiving TUD training and organizational change technical assistance versus 7 agencies receiving TUD training only. This 5-year trial will be completed in April 2021. The Addressing Tobacco Through Organizational Change (ATTOC) model includes 9 months of organizational change technical assistance, TUD training, and leadership support. Environmental Scans and Monthly Dashboards track agency changes. Staff and patient outcomes are assessed, including Smoking Knowledge, Attitudes and Services (S-KAS) for Clients and Smoking Knowledge, Attitudes, and Practices (S-KAP) for Staff.
Results: Preliminary data analysis of 10 sites is on 181 staff (44 smokers; 136 female, mean age 41, SD 11.7), 482 clients (481 smoker; 210 female, 272 male; mean age 45, SD 11.66; 16 cigarettes per day, SD=12.1), and Environmental Scan scores at 5 ATTOC sites which showed 23% improvement in 3 months (1.6 to 2.75 / 5), including sub-score increases related to patient care, chart documentation, staff recovery, environmental restrictions, policies, and environmental signage and support. Dashboard scores demonstrated parallel dramatic increases

at ATTOC sites in counseling or brief intervention by providers, referrals to community resources (quit line, etc.), CO meter use, and medication treatment.
Conclusions: Organizational change interventions can effectively change the culture, support leadership, and change clinician behavior to enhance integrating tobacco use disorder treatment into mental health and addiction treatment. Implementing this intervention could reduce health disparities by helping individuals reduce or stop their tobacco use. More dissemination and implementation science research is recommended.

PROOF-OF-CONCEPT STUDY OF TOLCAPONE IN WOMEN SMOKERS

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Abstract Detail: Human
Drug Category: Nicotine/Tobacco
Topic: Treatment
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Novel smoking cessation treatments, tailored for women smokers, are needed. We found in female, but not male smokers, presence of the high catechol-O-methyltransferase (COMT) enzyme activity genetic variant was associated with more severe withdrawal and smoking urges following overnight abstinence. Therefore, inhibition of COMT enzyme activity may ameliorate abstinence-related aversive symptoms, particularly in women. The aim of this phase I, proof-of-concept study was to assess whether the COMT inhibitor, tolcapone, would be superior to placebo in reducing withdrawal and smoking urges during abstinence, and reducing smoking behavior and subjective reinforcement from smoking in a laboratory paradigm (following abstinence), in women smokers.
Methods: A double-blind, placebo-controlled study of the COMT-inhibitor tolcapone was performed in women smokers only (N=32 starters, 29 completers). Participants completed a baseline assessment (ad libitum smoking, no medication), then were randomized to 8-days of tolcapone (100mg three times a day) or placebo (days 1 to 5: smoke ad libitum; night of day 5 to day 8: 60 hrs. abstinence). Withdrawal, craving, cognitive function, laboratory smoking choice behavior and subjective reinforcing effects of smoking were assessed at End-of-Trial (medication day 8, 60 hrs. abstinence).
Results: Interactions reflected trends towards greater reductions in smoking urges and withdrawal symptoms, significantly greater reductions in cigarette reinforcing effects (e.g., 'feel cigarette effects', 'want more'), and significantly greater improvements in cognitive function in the tolcapone (versus placebo) group at End-of-Trial (versus baseline). The tolcapone group earned more than placebo in the laboratory Smoking Choice Paradigm, during which participants were given tokens and could 'earn' more by choosing to keep cash-value tokens rather than 'spend' them on puffs of own-brand cigarettes.
Conclusions: Findings supported the hypotheses: tolcapone reduced smoking urges, withdrawal symptoms, smoking behavior, and subjective reinforcement from smoking in women. Additional research is needed into tolcapone as a potential cessation aid in women.

Perinatal

IMPACT OF CANNABIS USE IN WOMEN WITH OPIOID USE DISORDER ENROLLED IN BUPRENORPHINE MAINTENANCE TREATMENT

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Perinatal
Abstract Category: Original Research
Designation: M.D.

Abstract: Aim: As more states are legalizing medical marijuana, cannabis use is increasing with risk perception decreasing. Previous studies have evaluated various effects of cannabis use in different populations; however, to date, there is no research focused on pregnant women with opioid use disorder (OUD) enrolled in opioid agonist therapy (OAT). In this study we examined the associations between cannabis use and depression in pregnant women with OUD and how these variables affect opioid use.
Methods: Pregnant women with OUD followed in an academic ambulatory clinic were included in a retrospective chart review from intake to 3 months postpartum. At each visit, Beck Depression Inventory (BDI), a current list of medications and observed urine drug screens (UDS) were collected. Relapse/lapse was defined as an UDS positive for opioids. Our primary variables were UDS positive for cannabis, antidepressant use and BDI score. We calculated mean values of each variable for every woman across all weeks of treatment and used Spearman partial correlations to evaluate any associations between the variables.
Results: The final cohort consisted of 122 women with 79.5% Caucasian and an average age of 29 years. 28.7% of women tested positive for cannabis during treatment and was weakly associated with opioid lapse (RHO=0.183, p=0.047). However, when controlling for depression, this relationship was no longer significant (RHO=0.102, p=0.94). Cannabis use was associated with higher depressive (BDI) scores (RHO=0.217, p=0.019) and when controlled for opioid and antidepressant use, this association became more significant (RHO=0.293, p=0.001).
Conclusions: Cannabis use among pregnant women receiving treatment for OUD is associated with higher levels of depressive scores. We did not show a correlation between cannabis use and lapse of opioid use after controlling for depression. Further work should explore the impact of antidepressant treatment on cannabis use in high risk populations.

GABAPENTIN EXPOSURE AND THE TIME COURSE OF NEONATAL ABSTINENCE SYNDROME AMONG METHADONE-EXPOSED NEONATES

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Abstract Detail: Human

Drug Category: Polydrug (i.e. Use of more than one drug combination)
Topic: Perinatal
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Gabapentin use is common among individuals receiving medications for opioid use disorder (OUD), including pregnant women. We recently reported that maternal gabapentin use in the birth trimester was significantly associated with neonatal pharmacotherapy for neonatal abstinence syndrome (NAS). In the present study, we explored whether the time course of NAS was different between methadone-exposed infants with and without third trimester gabapentin exposure.
Methods: Data were extracted from medical records of women who delivered in 2017 while receiving comprehensive treatment for OUD, including methadone, at a single, university-affiliated treatment center. Maternal pregnancy, methadone dose at delivery, and use of drugs during pregnancy, and neonatal sex, birthweight, gestational age at delivery, and Apgar scores were extracted. Use of gabapentin and other drugs was defined as having a prescription or positive urine toxicology in the birth trimester. NAS was assessed using the MOTHER scoring system, beginning around 2 hours after birth and every 4 hours until discharge. Scores were averaged in 4-hour bins and only the first 120 hours of scoring were included in the present analyses. Maternal and neonatal characteristics were compared between gabapentin-exposed and non-exposed neonates using chi-square and t-tests. NAS scores were analyzed with a two-way ANOVA (gabapentin exposure x time). Statistical significance was determined at $p < .05$.
Results: Gabapentin-exposed (N=5) and non-exposed (N=50) neonates did not differ in any maternal or neonatal characteristics. There were significant main effects of gabapentin exposure ($p = .010$) and time ($p < .001$) on NAS scores; scores in both groups increased significantly over time, and mean scores were higher among gabapentin-exposed neonates. There was no significant interaction between gabapentin exposure and time.
Conclusions: Gabapentin exacerbates NAS among methadone-exposed neonates. Scores follow a similar time course but reach a higher peak among gabapentin-exposed infants. Future research should examine gabapentin interactions with other maternal medications for OUD.

RE-EMERGENCE OF METHAMPHETAMINE: OBSERVATIONS FROM A HIGH-RISK PRENATAL POPULATION

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Abstract Detail: Human
Drug Category: Stimulants
Topic: Perinatal
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: The U.S. DEA reported the seizure of 30,081 kg of methamphetamine (MA) along the Mexican border in 2017, which represents a 255% increase since 2012 (DEA, 2018). Coupled with increases in purity, decreases in cost per pure gram, and adulteration with fentanyl, a nationwide cause for concern exists in the wake of the ongoing opioid epidemic (DEA, 2018). Prenatal exposure to MA represents an understudied negative long-term public

health concern for our most vulnerable population (ACOG, 2011). The aim of this presentation is to report the prevalence and measured concentrations of MA observed in human umbilical cord tissue segments (UC) received at a national commercial reference laboratory.
Methods: A secondary analysis of a UC toxicology database between 2015 and 2019 was performed to test if trends reported by DEA would be observed using UC as a means of surveillance. The medians of the measured concentrations and positivity rates for MA for each quarter were calculated and plotted.
Results: Between January 2015 and October 2019, 262,571 UC specimens were analyzed for the presence of MA by immunoassay initial test method (cutoff = 5 ng/g). There were 13,886 (5.2%) that contained detectable MA (Median = 121 ng/g, IQR: 35.5 ng/g, 258 ng/g) using a previously published liquid chromatography tandem mass spectrometry confirmation method (Jones, Rios, Jones, Lewis, & Plate, 2009). The quarterly positivity rates observed for MA in UC for this population increased from 3.2% to 6.1%. The median concentrations ranged from 105 ng/g to 140 ng/g with no apparent trend.
Conclusions: Over the past four years, an alarming increase of MA positive UC were observed. In the wake of the opioid epidemic, maternal MA use has quietly resurfaced as a national public health concern. These data demonstrate that improved efforts for primary prevention of maternal MA use is a continuing need.

MATERNAL POSTNATAL MARIJUANA CONSUMPTION INCREASES RISK FOR PRESCHOOLERS' IRRITABILITY

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Abstract Detail: Human
Drug Category: Marijuana/Cannabinoids
Topic: Behavior
Abstract Category: Original Research
Designation: M.A.

Abstract: Aim: This study examined the impact of prenatal exposure to maternal stress (a natural disaster) and cannabis use, as well as postnatal maternal cannabis use on preschoolers' attention, activity, and irritability.
Methods: A racially and ethnically diverse (12% White, 24% Black, 51% Latinx, 10% Asian, and 3% "Other") sample of children (N=828; 49.4% female) born to mothers recruited from NYC hospitals during pregnancy were followed until 4-years-old. 24% of mothers were exposed to Superstorm Sandy while pregnant. At baseline, pregnant women self-reported their marijuana and other drug use. Children were followed up at 3-years-old and again at age 4. Mothers self-reported their postnatal marijuana use and also completed the Behavioral Assessment System for Children-2, rating their child's inattention, hyperactivity, and irritability on a 4-point scale, Never/Rarely to Almost Always. Preschoolers were classified as High Inattention, Hyperactivity, or Irritability if they received a T score greater than or equal to 65 on the BASC-2 Inattention, Hyperactivity or Aggression scales, respectively, at either age 3 or age 4 years. Data were analyzed using logistic regression. All models controlled for child sex and maternal prenatal alcohol, cigarette, or cocaine use.

Results: 18% of pregnant women reported consuming alcohol, cigarettes, or cocaine when pregnant. 9.3% of mothers used marijuana prenatally and 20% postnatally. Maternal postnatal marijuana use increased the odds of children exhibiting high irritability during preschool, OR=4.16; 95% CI=1.01-17.09, p=.048. Compared to girls, boys were over 4 times more likely to show high levels of inattention symptoms during preschool, OR=4.37; 95% CI=1.45-13.88, p=.009. No other significant findings emerged.
Conclusions: Although subject to empirical examination, it could be that mothers who use marijuana in the postnatal environment are less sensitive, increasing risk for emotion regulation difficulties in their young children.

LASTING CONSEQUENCES OF THC OR NICOTINE E-CIGARETTE VAPOR INHALATION IN RATS: FROM BRAINS TO BEHAVIOR

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Abstract Detail: Animal Study
Drug Category: Marijuana/Cannabinoids
Topic: Behavior
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Evidence suggests that e-cigarette vapor exposure during early life may produce lasting behavioral changes in adulthood including addiction and depression. Preclinical investigations have confirmed that e-cigarette aerosol, with and without nicotine, poses a considerable risk to the developing nervous system. The acute and lasting effects of e-cigarette exposure will be critical for assessing harms and for providing understanding mechanisms for potential therapeutic targets.
Methods: Pregnant Wistar rats were repeatedly exposed to vaporized Δ9-tetrahydrocannabinol (THC; 100 mg/kg) or propylene glycol (PG) vehicle for up to 2 weeks. The offspring were tested for anxiety-like behavior using the elevated plus maze procedure. In a separate experiment, adult Wistar rats were exposed to e-cigarette aerosol and brains were analyzed for changes in neuroinflammatory function.
Results: Rats born to mothers exposed to THC vapor exhibited decreased time spent in the open arms compared to rats born to mothers exposed to PG vehicle, confirming the effects of prenatal e-cigarette exposure.
Conclusions: These findings suggest that e-cigarette vapor exposure may have lasting age-dependent effects on neuronal function and behavior.

CANNABIS USE, MEDICAL CANNABIS, USE DISORDER AND TREATMENT RECEIPT AMONG PREGNANT WOMEN, NON-PREGNANT WOMEN AND MEN

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[1]*Friends Research Institute,* [2]*Virginia Commonwealth University,* [3]*University of Maryland,* [4]*Kaiser Permanente Northern California*

Abstract Detail: Human

Drug Category: Marijuana/Cannabinoids
Topic: Perinatal
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: To determine the prevalence of cannabis use, cannabis use disorder (CUD) and addiction treatment receipt, among pregnant and non-pregnant women, and men.
Methods: Data from the National Survey of Drug Use and Health (2013-2018) were used. Prevalence of past month cannabis use, CUD and treatment receipt were analyzed for men, non-pregnant women and pregnant women, stratified by medical use. Chi-square statistics and unadjusted odds ratios described differences in population-weighted percentages among the three groups.
Results: Among those with past month cannabis use, pregnant women had twice the odds of using cannabis for medical reasons (OR = 2.0, 95% CI = 1.0, 4.1)) and 6.6 times the odds (OR= 6.6, 95% CI = 1.7, 25.3) of self-reporting dependence or abuse criteria compared to non-pregnant women. Pregnant women who reported past month use and any past year medical use were least likely to have CUD (4.0%) compared to non-pregnant women (11.8%) and men (21.0%) ($p < .001$). Among those with CUD, only 6% of pregnant women and 4% of both men and non-pregnant women reported past year treatment for CUD.
Conclusions: Among people with past month cannabis use, pregnant women are more likely to self-report cannabis dependence or abuse but no more likely to meet DSM CUD criteria. Although pregnant women are supposed to receive preferential access to drug treatment, there is no evidence that pregnant women with CUD receive preferential access to care. Greater attention is needed to the role of medical cannabis in pregnancy and in identifying and removing barriers to CUD treatment.

INCREASING EFFECTIVE CONTRACEPTIVE USE AMONG WOMEN RECEIVING MEDICATION FOR OPIOID USE DISORDER AND AT RISK FOR UNINTENDED PREGNANCY

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Behavior
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Nearly 80% of opioid-exposed pregnancies are unintended, due in part to alarmingly low rates of effective contraceptive use among opioid-using women (<10%). We developed an intervention to increase prescription contraceptive use by women receiving medication for opioid use disorder (mOUD). Usual care in many mOUD clinics involves distribution of contraceptive information and referrals to community family planning providers. The intervention adds (1) the World Health Organization's (WHO) contraception protocol and (2) financial incentives for attendance at follow-up visits. Pilot data strongly

supported the efficacy of this intervention, with 5-fold higher rates of self-reported prescription contraceptive use in the experimental vs. control conditions at the end of the 6-month intervention (94% vs. 13%). A fully randomized controlled Stage II trial was conducted to rigorously evaluate the efficacy and cost-effectiveness of the different components of this innovative intervention.
Methods: Women receiving mOUD and at risk for unintended pregnancy (N=138) were randomly assigned to one of three study conditions: (1) usual care; (2) usual care+WHO contraception protocol; or (3) usual care+WHO contraception protocol+financial incentives for attendance. The primary outcome was verified prescription contraceptive use at the end of the 6-month intervention. Secondary outcomes included verified use at the 12-month follow-up and unintended pregnancies. Cost-effectiveness was measured by incremental cost-effectiveness ratios (ICERs).
Results: There was a graded effect, with 10% vs. 29% vs. 55% verified prescription contraceptive use at 6 months across the three conditions, respectively; all pairwise comparisons were statistically different ($p<.05$). At the 12-month follow-up, verified contraceptive use was also graded (6% vs. 25% vs. 42%, respectively). The percent of unintended pregnancies over 12 months was 22% vs. 17% vs. 2%, respectively. ICERs also suggest both interventions are more cost-effective than usual care.
Conclusions: The experimental interventions increase prescription contraceptive use and are more cost-effective than usual care, but financial incentives provide added efficacy.

Policy

PATIENT AND PRESCRIPTION RISK FACTORS ASSOCIATED WITH THE DEVELOPMENT OF OPIOID USE DISORDER AND OVERDOSE AMONG YOUTH

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Adolescent
Abstract Category: Original Research
Designation: M.D.

Abstract: Aim: A small percentage of adolescents and young adults prescribed an opioid will progress to a use disorder. We identified patient and prescription risk factors associated with opioid misuse, use disorder, or overdose (collectively, "opioid-related complications") during the year after youth were dispensed their first documented opioid prescription.
Methods: We conducted a retrospective cohort study of 3,301,610 commercially insured youth aged 11-25 years who were dispensed their first documented opioid prescription between January 1, 2006 and December 31, 2016. Eligible youth had ≥6 preceding months without a diagnosis or treatment suggestive of an opioid-related complication, and ≥12 months of continuous coverage after the opioid was dispensed. We used multivariable logistic regression to examine patient and prescription characteristics associated with opioid-related

complications during the year after the opioid was dispensed. Patient factors included age, sex, urban/rural location, mental health conditions, and acute/chronic pain diagnoses; prescription factors included short- vs. long-acting formulation, daily dose in morphine milligram equivalents (MME)/day, and duration.
Results: Among eligible youth, median age was 18 years (interquartile range [IQR], 16-21) and 56% were female. Median opioid dose and duration prescribed were 33 MME/day (IQR, 23-50) and 3 days (IQR, 3-5), respectively. Overall, 10,040 (0.3%) individuals developed an opioid-related complication in the year following their prescription. Factors associated with opioid-related complications included male sex (adjusted odds ratio [aOR] 2.05, 95% confidence interval [CI] 1.96-2.14), mood/anxiety disorder (aOR 4.71, CI 4.51-4.93), other substance use (aOR 21.35, CI 20.37-22.38), long-acting opioid formulation (aOR 3.41, CI 2.76-4.21), dose >120 MME/day (aOR 1.21, CI 1.09-1.34), and duration ≥15 days (aOR 2.13, CI 1.95-2.32).
Conclusions: To prevent opioid-related complications following a prescription, it may be prudent to screen youth for mood/anxiety disorders and substance use, and to ensure prescriptions are for short-acting opioids and use the lowest effective dose and duration.

PREGNANCY, STATE POLICIES, AND WOMEN'S ACCESS TO MEDICATION FOR OPIOID USE DISORDER (MOUD): A MULTILEVEL ANALYSIS

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Policy
Abstract Category: Original Research
Designation: M.S.

Abstract: Aim: Prior research has found gender differences in access to substance use disorder treatment, including medication for opioid use disorder (MOUD), but the reasons are poorly understood. Pregnancy may provide distinct opportunities and pressures to pursue MOUD, as well as distinct barriers. This study examined the effects of pregnancy, variation in Medicaid policies regarding MOUD, laws that criminalize substance abuse during pregnancy, mandatory reporting laws for substance-exposed newborn infants, on women's access to MOUD.
Methods: Using the Treatment Episode Data for Discharge (TEDS-d, 2014-2017), we identified the initial treatment episodes of women aged 18 to 44 with OUD (n=151,929). We conducted logistic regression analysis to assess the effects of individual (pregnancy status, age, race, and education level) and multilevel logistic regression analysis to assess the effects of contextual-level (Medicaid expansion status, laws that criminalize substance use and/or mandates reporting) predictors on MOUD access (methadone and/or buprenorphine). Model 3 included both levels.
Results: A total of 15% episodes noted the use of MOUD at admission. The odds of MOUD access is threefold greater for pregnant women compared to other women ($p<0.01$). Individual-level factors (being older, black, other racial/ethnic minority, lower levels of formal educational attainment) were also associated with increased odds of accessing MOUD ($p<0.01$). Adjusting for individual-level factors, a greater proportion of states in the Northeast had increased odds of accessing MOUD, relative to other regions in the US. When adjusting for state-level factors,

the state's Medicaid expansion status and criminalization laws increased the odds of MOUD access ($p<0.05$) while the reporting mandate was not associated with access to MOUD.
Conclusions: Access to MOUD for reproductive age women involves health inequity, state-policy, and economic and social factors. Identifying individual- and state-level factors associated with access to MOUD allows for the development of targeted state-level interventions to improve access for women in need of services.

MEDICATION-ASSISTED TREATMENT ASSOCIATED WITH POSITIVE JUSTICE OUTCOMES IN UNITED STATES' FIRST OPIOID INTERVENTION COURT

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Treatment
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: In response to the opioid epidemic, the nation's first Opioid Intervention Court (OIC) was established in Buffalo, New York in May 2017. In contrast to traditional drug treatment court, a primary component of OIC is linkage to medication-assisted treatment (MAT). Although MAT is now considered a standard of care in the treatment of opioid use disorder, many drug treatment courts still rely on an abstinence-based approach. It is not yet known if MAT is associated with positive justice outcomes.
Methods: Data were abstracted from the court records of individuals who had an OIC case closed between May 2017 and September 2019 (N = 384). Of these individuals, 52.3% received MAT during OIC. To be eligible for OIC, individuals must have been arrested for a non-violent offense and reported opioid abuse. We used separate logistic, negative binomial, and fractional regression models to examine the effects of receiving MAT on the following justice-related outcomes: graduating from OIC, being on warrant, length of stay in OIC, and proportion of drug toxicology tests passed. Final models controlled for sex, age, and race-ethnicity.
Results: Receiving MAT during OIC was significantly associated with a greater likelihood of graduating from OIC (OR = 3.34, 95% CI: 2.06, 5.45; $p < 0.001$), a lower likelihood of being on warrant (OR = 0.52, 95% CI: 0.32, 0.81; $p < 0.01$), a greater length of stay in OIC (RR = 1.43, 95% CI: 1.19, 1.72; $p < 0.001$), and a greater proportion of drug toxicology tests passed (OR = 2.17, 95% CI: 1.42, 3.30; $p < 0.001$).
Conclusions: Findings suggest that access to MAT is an essential component to improving justice-related outcomes in drug treatment court programs. Additional research is needed to fully evaluate the effectiveness of the OIC model, including its impact on treatment and health outcomes.

DO MEDICAL CANNABIS LAWS UNDERMINE EVIDENCE-BASED CARE FOR OPIOID USE DISORDER?

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Abstract Detail: Human
Drug Category: Marijuana/Cannabinoids
Topic: Policy
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Identify the impact of adding opioid use disorder (OUD) as a qualifying condition for medical cannabis on dispensary advertisements. We hypothesized that more cannabis dispensaries in states with OUD as qualifying condition would advertise cannabis as a treatment for OUD, compared to adjacent states with medical cannabis programs but without OUD as a qualifying condition.
Methods: We conducted a mixed-methods study of online content by cannabis dispensaries. We triangulated government and industry websites to identify dispensaries in Northeastern states where OUD was a qualifying condition (PA, NY, NJ) and adjacent states (CT, DE, MD, OH, WV). We searched dispensary websites, Facebook, and Twitter for six keywords ("opioid," "opioids," "addiction," "methadone," "buprenorphine," "suboxone"). We qualitatively coded advertisement content as saying that cannabis can a) treat OUD, b) replace opioid substitution treatment (OST), c) be an adjunctive to OST, and/or d) replace opioids for chronic pain or other indications, or e) none. Using one-tailed Z-tests, we compared the proportion of PA, NY, NJ dispensaries making these claims to adjacent states.
Results: We identified 165 unique dispensaries, 44 in states with OUD as a qualifying condition and 121 in adjacent states. In PA, NY, and NJ, 59% of dispensaries said cannabis could treat OUD, versus 26% in adjacent states ($p<0.01$). In PA, NY, and NJ, 19% said cannabis could replace OST (versus 5% in adjacent states, $p<0.01$); 30% mentioned cannabis as an OST-adjunctive (versus 1%, $p<0.01$).
Conclusions: More dispensaries in states where OUD was a qualifying condition for medical cannabis claimed that cannabis could treat OUD, and some encouraged patients to replace OST with cannabis. Such claims – which lack medical evidence – could worsen OUD outcomes if people opt for cannabis over evidence-based treatments. States considering adding OUD as a qualifying condition for medical cannabis may instead enact policies to increase access to OST.

ANALYSIS OF DRUG INDUCED HOMICIDE PROSECUTIONS AS A DRUG OVERDOSE PREVENTION MEASURE

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Prevention
Abstract Category: Original Research
Designation: M.A.

Abstract: Aim: In the past few years, the overdose crisis has sparked an increase in drug induced homicide (DIH) laws and prosecutions. Although the DIH prosecutions are presented as an overdose prevention measure, their impact has not been empirically assessed. Using

datasets that contain information collected from media reports about DIH prosecutions, we estimate the impact of an increase in DIH prosecution media alerts on fatal overdoses by state between 2000 - 2017.
Methods: We conduct the analysis for 43 states (Alaska, Montana, Nebraska, North Dakota, South Dakota, Vermont, and Wyoming excluded due to missing data) using logistic regression modeling, while controlling for relevant policy interventions (naloxone access laws, 911 Good Samaritan Laws, Medicare Expansion, medical and recreational cannabis laws, and prescription drug monitoring policies). Time effects are smoothed and can vary by state.
Results: From the analysis, we see that an increase in prosecution media alerts leads to an approximately 7.7% increase in overdose deaths, which is statistically significant. Further analysis suggests that in the 43 states analyzed during 2000-2017, there was an average of approximately 1,790 deaths attributable to DIH prosecutions each year.
Conclusions: The analysis suggests that DIH prosecutions actually increase the risk of overdose, which contradicts its stated aims of preventing overdoses. Further assessment of the pathways of the policy impact is needed.

PURCHASING VAPING PRODUCTS IN THE ILLEGAL EXPERIMENTAL TOBACCO MARKETPLACE

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Abstract Detail: Human
Drug Category: Nicotine/Tobacco
Topic: Policy
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Banning sales of vaping products may have unintended outcomes, such as increased demand for illegal products. The present study experimentally examined the effects of implementing a vaping ban and a flavored vaping ban on the probability of purchasing vaping products in an illegal marketplace as the price of conventional cigarettes increased in a legal marketplace.
Methods: A within-between subject's design was used to assess marketplace preference of three groups (cigarette smokers, e-cigarette users, dual users) under three conditions (no ban, vaping ban, flavored vaping ban). A crowdsourced sample of tobacco/nicotine users (n=150) completed hypothetical purchasing trials in an Experimental Tobacco Marketplace. Before every trial, participants were presented with the option to purchase in a legal experimental tobacco marketplace (LETM) or an illegal experimental tobacco marketplace (IETM), as the price of legal cigarettes increased. A range of tobacco products such as cigarettes, dip, snus, nicotine gum, and nicotine lozenges were always available in the LETM. In the no ban condition, vaping products were available in both LETM and IETM. In the flavored vaping ban condition, tobacco flavored vaping products were available in the LETM, and other flavored vaping products were available in the IETM. In the vaping ban condition, vaping products were only available in the IETM.
Results: Participants from all groups were more likely to purchase from the IETM when product availability in the LETM was more restricted. Furthermore, cigarette smokers only and

dual users' preference for marketplace was more price sensitive compared to e-cigarette users only, such that these participants were more likely to buy vaping products in the IETM as the price of cigarettes in the LETM increased.
Conclusions: This study suggests that limiting or banning vaping products from the marketplace or increasing the price of cigarettes may shift preference towards purchasing vaping products in the illegal marketplace.

INVESTIGATING CONCERNS ABOUT NALOXONE RECEIPT AND RISK COMPENSATION IN LONG-TERM OPIOID THERAPY: BASELINE FINDINGS FROM THE JUST-IN-CASE TRIAL

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Prevention
Abstract Category: Original Research
Designation: F.A.C.P., M.D., M.P.H., M.S.

Abstract: Aim: Naloxone is an effective opioid antagonist that reverses overdoses. A barrier to expanding access to naloxone, however, is the concern that naloxone could lead to increased opioid risk behaviors knowing that a potentially fatal overdose could be reversed (i.e., risk compensation). Thus, the aim of this observational, longitudinal analysis was to examine whether individuals prescribed long-term opioid therapy who were dispensed naloxone were more likely to report opioid risk behavior than those who were not dispensed naloxone.
Methods: The study population comprised patients recruited for a randomized intervention trial designed to expand access to naloxone – the Just-in-Case trial. All patients were prescribed long-term opioid therapy while receiving care in an urban, safety-net healthcare system. At recruitment, participants were administered a baseline survey that used the following validated scales: Opioid-Related Behaviors in Treatment scale (ORBIT), pain intensity (PROMIS) and opioid overdose knowledge (Rx-OOKS). Past-year receipt of naloxone was assessed using pharmacy dispensing data. We conducted a one-way analysis of variance (ANOVA) to examine the association between receipt of naloxone and risk behavior, controlling for age, gender, race/ethnicity, prior diagnosis of opioid use disorder, knowledge, and pain intensity.
Results: A total of 333 participants were recruited into the trial and 323 completed the baseline survey ORBIT instrument. The mean age was 57.7 years (SD=10.6), 52.6% were female, 18.9% were African American, and 36.8% were Hispanic. The mean risk behavior score was 1.34 (SD=1.98), and 19.5% of the participants had received naloxone prior to completing the baseline survey. In the ANOVA analysis, receipt of naloxone was not associated with risk behavior ($p=0.13$). Increased pain intensity was the only variable significantly associated with increased risk behavior ($p=0.02$).
Conclusions: These observational, longitudinal findings do not support the concern that expanded access to naloxone will create a moral hazard among patients taking long-term opioid therapy.

Social Factors

PEER INFLUENCES ON ADOLESCENTS' INTENTIONS FOR FUTURE ELECTRONIC NICOTINE DELIVERY SYSTEM USE

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Abstract Detail: Human
Drug Category: Nicotine/Tobacco
Topic: Adolescent
Abstract Category: Original Research
Designation: M.A.

Abstract: Aim: Electronic nicotine delivery system (ENDS) use among teens has skyrocketed. Evidence suggests that peer influence is a primary factor contributing to adolescents' use propensity. A more precise understanding of how peers impact future ENDS use intentions could identify potential intervention and/or prevention targets.
Methods: We assessed psychosocial variables mediating the relationship between peer ENDS use and future use intentions at wave 1 of a longitudinal study among a sample (N=248) of high-school students (14-17 years old, M=14.95 0.67, Hispanic/Latinx: 84.7%). Participants completed items from the Monitoring the Future survey to assess perceived peer use, items from the Population Assessment of Tobacco and Health (PATH) survey to assess their own use intentions, the Resistance to Peer Influence Scale, and the E-cigarette Attitudes Survey. We estimated a serial multiple mediator model to investigate direct and indirect effects of perceived peer use on intentions to use (one year from now). Specifically, we expected that peer ENDS use would impact resistance to peer influence, which in turn would impact positive ENDS attitudes, and ultimately influence ENDS use intentions. Bootstrapping procedures were used to estimate the statistical significance of indirect effects.
Results: Findings indicate a negative association between peer ENDS use and resistance to peer influence (β=-0.20, p=0.001), a negative association between resistance to peer influence and ENDS attitudes (β=-0.18, p=0.003), and a positive association between ENDS attitudes and use intentions (β=2.78, p<0.001). Both the direct (β=0.15, p<0.001) and indirect (β=0.010; 95%CI=[0.002, 0.024]) effects were significant indicating the association between peer use and future ENDS use intentions was partially mediated by resistance to peer influence via ENDS attitudes.
Conclusions: These outcomes suggest that social influences can impact teens' future ENDS use intentions by modulating ENDS attitudes. Interventions facilitating resistance to peer influence among teens with ENDS using peers may be a viable prevention target.

PATERNAL MORPHINE EXPOSURE CAUSES MALADAPTIVE BEHAVIOR IN MALE PROGENY

Andre B. Toussaint[*1], Alexandra Ellis[2], Angela Bongiovanni[1], Samuel Schumacher[1], Hannah Mayberry[1], Gregory Carr[3], Mathieu Wimmer[1]*

[1]*Temple University,* [2]*University of Pennsylvania,* [3]*Lieber Institute for Brain Development*

Abstract Detail: Animal Study
Drug Category: Opiates/Opioids
Topic: Behavior
Abstract Category: Original Research
Designation: M.A.

Abstract: Aim: Previous studies have shown that paternal lifetime experiences can affect the behavior and physiology of their offspring. According to recent estimates, 5 million children have fathers who abuse drugs. Given the nationwide opioid addiction crisis, a better understanding of the long-term impact paternal drug-exposure has on subsequent generations may lead to better therapeutic approaches for substance abuse. Here, we investigated the influence of paternal morphine exposure on the behavior of future progeny.
Methods: Adult male rats self-administered morphine for 60 days; controls received saline. Following this chronic morphine regimen, each sire was bred with a drug-naïve female to produce first generation (F1) offspring (morphine-sired or saline-sired). We assessed social play behavior – a rewarding activity important for social and cognitive development - in adolescent F1 progeny. In adulthood, male and female F1 progeny were allowed to self-administer morphine, cocaine or sucrose.
Results: Morphine-sired male offspring played less than saline-sired controls. Specifically, pinning which is the most characteristic posture in social play during this developmental period was considerably reduced in male offspring produced by morphine-exposed sires. In adulthood, morphine-sired male progeny took more morphine than their respective controls. Morphine-sired male offspring also worked harder to receive infusions of morphine, under a progressive ratio schedule. This phenotype seemed to be drug-specific in that sucrose or cocaine self-administration were not altered by paternal morphine history in male or female F1 progeny.
Conclusions: Together, these results demonstrate that paternal morphine exposure can have deleterious consequences in progeny. Previous studies have shown that social play and morphine taking are regulated by opioid signaling. Since both behaviors are impacted by paternal morphine exposure, it is plausible that opioid signaling is disrupted in the brain of morphine-sired male progeny. Our findings add to the evidence that environmental perturbations experienced by fathers can result in alterations in the behavior of offspring.

PEER-INDUCED REMIFENTANIL SEEKING IN MALE AND FEMALE RATS

Lindsey Hammerslag[*1], Michela Carbone[2], Samantha Malone[1], Scott DiMeo[1], Michael Bardo[1]*

[1]University of Kentucky, [2]University of Cagliari

Abstract Detail: Animal Study
Drug Category: Opiates/Opioids
Topic: Behavior
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Re-association with drug-associated peers contributes to relapse in humans, and we have recently found that exposure to cocaine-associated peers triggers reinstatement in

rats. Here we extend these findings to opioids by pairing one peer with the fast-acting opioid remifentanil and another peer with saline.
Methods: Male (n = 5) and female (n = 6) rats received 28 days of twice-daily self-administration. Each day, remifentanil (6 µg/kg/infusion) was available during one session in the presence of one same-sex peer (S+) and saline was available in another session in the presence of a different peer (S-). During the first 7 days, we autoshaped rats for 20-min prior to each 60-min fixed ratio 1 (FR1) session. Subsequently, rats received 7 days at FR1, 7 days at FR3, and 7 days at FR5. Following extinction, we tested reinstatement to the S+, S- or no peer. Rats were perfused 90-min after the start of the 3rd test for later immunohistochemical analysis of cFos.
Results: Following pre-training, rats increased active lever presses for remifentanil as the FR increased (lever*drug*FR interaction: $F_{1,871} = 18.6$, $p < 0.001$). Latency to earn the first infusion also increased with FR for saline only, with faster responding for remifentanil at FR5 (FR*drug interaction: $F_{2,20} = 3.78$, $p = 0.041$). During reinstatement, there was increased active, but not inactive, lever pressing in the presence of either peer (peer*lever interaction: $F_{2,20} = 7.5$, $p = 0.004$); importantly, the remifentanil peer elicited more active lever presses than the saline peer ($t_{20} = 3.14$, $p = 0.014$).
Conclusions: These results extend our previous findings with cocaine, demonstrating that rats will learn to associate a peer with remifentanil availability and will later engage in peer-induced opioid seeking. Although either peer elicited reinstatement, re-exposure to the remifentanil-associated peer had the greatest impact.

THE ASSOCIATION BETWEEN SOCIAL ISOLATION AND COCAINE USE IN A DIVERSE COMMUNITY SAMPLE

Nathan Smith[1], Laura Gonzalez Paz[1], Linda Cottler[1]*
[1]*University of Florida*

Abstract Detail: Human
Drug Category: Stimulants
Topic: Prevention
Abstract Category: Original Research
Designation: ALM

Abstract: Aim: Cocaine use is a significant public health problem that can lead to severe physical, psychiatric, and financial consequences that can also lead to cocaine use disorder1. Social isolation has been linked to cocaine use in animal models2,3 as well as human children4 and adults5. However, data on multiple measures of social isolation and cocaine use in community samples is scarce.
Methods: To address this, HealthStreet, a community outreach initiative at the University of Florida assesses community members for health conditions and links them to needed medical and social services. Community Health Workers meet with community members at shopping plazas, laundromats, and other places where people congregate, to assess health needs and concerns and offer opportunities to enroll in health research. The sample of 11,058 were stratified into those who never used cocaine, those who used in their lifetime but not in the past 30 days, and those who used in the past 30 days. Data were also collected on measures of social isolation related to communication, social support, living situation, family, and employment. We then evaluated the relationship between each aspect of social isolation and cocaine use.

Results: Among the sample, 81% reported never using cocaine, 17% used cocaine but not in the past 30 days, and 2% used in the past 30 days. Significant differences between membership in the three groups were found for communication (text messaging), social support (having someone to talk to and to rely on), living situation (living with others), family status (being married and having children) and being employed.
Conclusions: Several social isolation measures were significantly associated with cocaine use. Further research should examine the temporal order of the relationship between the variables to identify avenues for intervention.

Stimulant/Medication Development

PTPRD: DRUGGING A NOVEL ANTI-ADDICTION TARGET

George Uhl[1], Ian Henderson[2], Maria Martinez[2], Thomas Prisinzano[3], David Johnson[4], Wei Wang[5]*

[1]*University of New Mexico Health Sciences Center,* [2]*New Mexico VA,* [3]*University of Kentucky,* [4]*University of Kansas,* [5]*University of Arizona*

Abstract Detail: Human
Drug Category: Stimulants
Topic: Treatment
Abstract Category: Original Research
Designation: M.D., Ph.D.

Abstract: Aim: Human genetics, mouse genetics and initial pharmacology with our partially-selective inhibitor, 7-BIA, all support PTPRD (receptor type protein tyrosine phosphatase D) as a novel, druggable antiaddiction target. We aim to improve understanding of the PTPRD D1 phosphatase domain structure, function and interactions with small molecules and physiological substrates in order to develop improved PTPRD inhibitors that will reduce reward from addictive substances with few off target interactions. Improved understanding of PTPRD function will also provide novel markers for brain target engagement.
Methods: We have validated a dozen in vitro assays for function of PTPRD and comparison phosphatases, constructed molecular models for these phosphatases, docked 7-BIA and other inhibitors and conducted in silico screening for 7-BIA analog potencies and selectivities. We have improved syntheses of 7-BIA (from 14 step to 8 step) and synthesized and tested 6- and 7-position substituted analogs. We have synthesized phosphopeptide candidate physiological PTPRD substrates and docked these in silico. We have validated Western analyses of tyrosine phosphorylated kinases as candidate brain markers for PTPRD target engagement.
Results: We have identified good fits between in silico and in vitro data comparing 7-BIA potencies at these dozen expressed recombinant phosphatases. We have identified effects of 6- and 7-position substitutions on potencies of 7-BIA analogs. We have identified pY15CDK5 as a good PTPRD substrate based on competition for pNPP hydrolysis and release of orthophosphate from this phosphopeptide. pY15CDK5 phosphorylation serves as a promising candidate marker for brain target engagement.
Conclusions: Small molecule and phosphopeptide data have enriched our understanding of PTPRD as a target for novel antiaddiction therapeutics, provided increasingly validated silico modeling and provided a novel candidate measure of in vivo target engagement. Previous

implication of CDK5 in addiction mechanisms and our current findings of its regulation by PTPRD provide a novel explanation for PTPRD addiction associations in humans and mouse models.

PSILOCYBIN MECHANISMS OF ACTION FOR SMOKING CESSATION: PRELIMINARY DATA FROM A RANDOMIZED CONTROLLED TRIAL

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[1]Johns Hopkins University School of Medicine, [2]Center for Psychedelic and Consciousness Research, Johns Hopkins University School of Medicine

Abstract Detail: Human
Drug Category: Nicotine/Tobacco
Topic: Mechanisms of Action
Abstract Category: Original Research
Designation: M.A., Ph.D.

Abstract: Aim: Psilocybin has shown safety and feasibility as a potential adjunct to traditional smoking cessation behavioral interventions. However, mechanisms of action psilocybin-facilitated smoking cessation remain unclear.
Methods: In an ongoing clinical trial, 53 treatment-seeking cigarette smokers were randomly assigned to receive a single high-dose (30 mg/70 kg) of psilocybin (n=26) on their target quit date (TQD), or begin an 8-10 week course of nicotine patches (n=27) after 24 hours of smoking abstinence. Both groups received matched cognitive behavioral therapy for smoking cessation. Participants completed validated measures of craving, withdrawal, confidence to abstain, and temptation to smoke at screening, 1 day, and 1-week post-TQD.
Results: Independent samples t-tests showed no between group differences on scores of craving, withdrawal, confidence to abstain, or temptation to smoke at screening. However, 2-way ANOVA found significant differences over time in all four measures, and significant between group differences in confidence to abstain and temptation to smoke. Tukey's multiple comparisons showed significant reductions in anticipation of relief from withdrawal at 1 day and 1-week post-TQD, and craving at 1-week post-TQD in the psilocybin group, but not the patch group. Additionally, both groups showed significant decreases from screening in temptation to smoke and increases in confidence to abstain, though these differences were significantly greater in the psilocybin vs. patch group at both time points ($p<0.05$).
Conclusions: Psilocybin may improve smoking cessation treatment efficacy by reducing craving, temptation, and anticipation of relief from withdrawal, and enhancing confidence to abstain. Findings further support the role of psilocybin in facilitating smoking cessation via relevant psychological mechanisms, which warrant additional investigation.

4N-SUBSTITUTED-3,4-DICHLOROPHENYLACETAMIDE-9-(N)-PYRROLIDINE-PYRANOPIPERAZINE ANALOGS CHARACTERIZED AS NOVEL KAPPA OPIOID RECEPTOR AGONISTS IN MALE C57BL6 MICE

Ariel Ben-Ezra[*1], Brian Reed[1], Philip Pikus[1], Amelia Dunn[1], Mary Jeanne Kreek[1]*

[1]The Rockefeller University

Abstract Detail: Animal Study
Drug Category: Stimulants
Topic: Behavior
Abstract Category: Original Research
Designation: B.A.

Abstract: Aim: The kappa opioid receptor (KOR) is a potential target for the treatment of psychostimulant addiction. We have recently revealed that the sedative properties of KOR agonists correlate with KOR-mediated arrestin signaling, whereas other KOR endpoints such as prolactin release do not. We have developed a novel KOR scaffold, 3,4-dichlorophenylacetamide-9-(N)-pyrolidine-pyranopiperazine [PAPPP], with over 60 analogs synthesized (WuXi), five of the most promising of which we aimed to characterize in vivo.
Methods: Five novel KOR agonists were tested in adult male C57BL6 mice. Following training on the rotarod apparatus, animals were injected with compound (or vehicle: 10%ethanol, 10%Tween-80, 80%water), and tested at 0, 30, and 60 minutes. For the prolactin assay, mice housed in stress-minimized conditions were injected with vehicle or compound and serum prolactin levels were determined. In some experiments, animals were pretreated with the short-acting KOR antagonist LY2444296 to verify the effects are mediated by KOR. Tested analogs include the resolved stereoisomers of the non-substituted PAPPP, as well as racemic methyl-PAPPP, benzyl-PAPPP and cyclobutyl-PAPPP.
Results: One of the two PAPPP stereoisomers yielded significant sedation (90mg/kg) and showed significant prolactin release (10mg/kg,30mg/kg); the other isomer did not show prolactin release. Methyl-PAPPP (30mg/kg) yielded sedation and prolactin release (30mg/kg,90mg/kg). Benzyl-PAPPP and cyclobutyl-PAPPP were not sedative but caused significant increase in prolactin release (30mg/kg). Moreover, prolactin increase was blocked by pretreatment with LY2444296, indicating both compounds' effects are KOR mediated.
Conclusions: These chemical analogs cause significant effects in vivo, including prolactin release and rotarod-mediated sedation at certain doses, some of which could be blocked with a selective KOR antagonist. Further studies are necessary to determine the mechanism and the kappa specificity of these in vivo effects. Characterization of these compounds in additional behaviorally relevant assays is warranted.

Oral Communications II, Q&A - Treatment from Emergency Department/Hospital

3:30 p.m. - 4:30 p.m.

CTN-0079: IMPLEMENTING BUPRENORPHINE PROGRAMS IN HETEROGENOUS ED SETTINGS

Ryan McCormack[*1], John Rotrosen[1], Gail D'Onofrio[2], Phoebe Gauthier[3], Lisa Marsch[3], Abigail Matthews[4], Caroline Mulatya[4], E. Jennifer Edelman[2], Sarah Farkas[1], David Fiellin[2], William Goodman[5], Kristen Huntley[6], Randolph Knight[7], David Liu[6], Sarah Meyers-Ohki[1], Patricia Novo[1], Soo-Min Shin[1], stephen Wall[1], Kathryn Hawk[2]*

[1]NYU Langone School of Medicine, [2]Yale University School of Medicine, [3]Geisel School of Medicine at Dartmouth, [4]The Emmes Company, LLC, [5]Catholic Medical Center, [6]National Institute of Drug Abuse, National Institutes of Health, [7]Valley Regional Hospital

Abstract Detail: Human

Drug Category: Opiates/Opioids
Topic: Treatment
Abstract Category: Original Research
Designation: M.D.

Abstract: Aim: To evaluate the feasibility and impact of introducing emergency department (ED) clinical programs for buprenorphine initiation and referral in rural and urban settings with high need, limited resources, and different staffing structures.
Methods: This was a multicenter, implementation feasibility study with a 6-month evaluation period that began on the date each hospital approved its clinical protocol. It took place in New Hampshire at a critical access hospital and a community hospital with urban and rural catchment, and at a New York City public safety-net hospital. We employed Implementation Facilitation procedures and a participatory action approach combining mixed qualitative and quantitative inquiry with health record data to develop, introduce, evaluate, and refine clinical protocols and implementation strategies. A purposive sample of patients eligible to receive ED-initiated buprenorphine were enrolled to evaluate 30-day patient-level outcomes. Primary outcomes were descriptive (without formal hypothesis testing): to estimate the proportions who received buprenorphine amongst those eligible, and who were engaged in treatment at day 30.
Results: Within 4 months of IRB approval, site-specific clinical protocols were approved at each hospital. In the following 6 months, 134 unique patients were confirmed to be eligible and willing to receive ED-initiated buprenorphine, 112 (83.6%) of whom received it. Of the 46 enrolled patients, 40 received buprenorphine. Following their index ED-visit, 34 (73.9%) attended opioid treatment and 23 (50%) remained engaged in treatment on day 30 (via confirmed self-report). At the 30-day follow up visit, participants reported 1.3 days of opioid use in the last 7 days (from 4.3). Toxicology confirmed the presence of buprenorphine in 32/41 (78%). Measures of treatment satisfaction and changes in health quality were generally favorable.
Conclusions: The rapid adoption of ED-initiated BUP programs in these heterogeneous contexts with high rates of treatment initiation and 30-day retention supports continued study and implementation efforts in these non-traditional settings.

CHARACTERISTICS OF EMERGENCY DEPARTMENT PATIENTS WITH UNTREATED OPIOID USE DISORDER IN FOUR GEOGRAPHICALLY DIVERSE CITIES

Edouard Coupet[*1], Gail D'Onofrio[1], David Fiellin[1], Marek Chawarski[1], E. Jennifer Edelman[1], Patrick O'Connor[1], Patricia Owens[2], Shara Martel[2], Kathryn Hawk[2]*

[1]Yale University School of Medicine, [2]Yale University

Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Epidemiology
Abstract Category: Original Research
Designation: M.D., M.S.

Abstract: Aim: Emergency departments (EDs) are a critical setting to engage individuals with untreated opioid use disorder (OUD). To inform future implementation of ED-initiated

treatment of OUD, we sought to describe the sociodemographic characteristics of patients seeking and not seeking treatment presenting to geographically diverse urban EDs.
Methods: Using data from ED participants with untreated OUD enrolled during the observational period of an implementation-effectiveness study (CTN-0069), we performed a cross-sectional analysis of data collected from 2/2017-1/2019 from four EDs in Baltimore, New York, Cincinnati, and Seattle. We computed summary statistics reason for ED visit, demographic information, education, employment, housing status and substance use by urine toxicology testing and bivariate analysis based on whether or not participants came to ED seeking treatment.
Results: Among 396 individuals, 15% (60/396) came to the ED specifically for a referral for substance use treatment. Those seeking treatment were less likely to be white (43%;26/60) compared to non-white (57%;34/60); p=0.05. No differences in age, gender, education, insurance status or housing stability were detected between those seeking treatment and not seeking treatment. Overall participants had a mean age of 38.8 (SD+/-11.7) years and were 69% male. Approximately one-third had less than a high school education (142/396). Fifty-eight percent (230/396) of participants were unemployed. Over half of participants (220/396) reported housing instability. Those seeking treatment were less likely than those not seeking treatment to have toxicology positive for amphetamine (17%;10/60 vs 31%;102/334) and methamphetamine (23%;14/60 vs 39%;130/334) and more likely to be positive for opiates (93%;56/60 vs 81%;272/334) and fentanyl (66%;39/59 vs 49%;163/334); p<0.05.
Conclusions: ED patients seeking treatment for OUD were more likely to be non-white and have urine toxicology testing positive for fentanyl compared to those not seeking treatment. Overall, more than half the patients with OUD report unstable housing. Strategies to improve access to care and overcome barriers to treatment are needed.

TRAINING METHODS FOR EMERGENCY DEPARTMENT-BASED SUBSTANCE USE DISORDER RESEARCH: STRATEGIES FOR DEVELOPING COMPETENCIES IN RESEARCH STAFF

Phoebe Gauthier[*1], Sarah Meyers-Ohki[2], Amber Regis[2], Kathleen Bell[1], Soo-Min Shin[2], Kathryn Hawk[3], Nico Agosti[1], Dagmar Salazar[4], Ryan McCormack[2]*

[1]Geisel School of Medicine at Dartmouth College, [2]New York University School of Medicine, [3]Yale University, [4]The Emmes Company, LLC

Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Substance Use Disorder
Abstract Category: Program Descriptions
Designation: M.A., M.P.H.

Abstract: Aim: As emergency departments (EDs) across the country combat the opioid epidemic from the front lines, there is increased need for high-quality research on interventions for opioid and other substance use disorders (SUDs). Here we incorporate lessons learned from a multi-site implementation-feasibility study to offer considerations for team training and describe personnel competencies that may contribute to successful implementation of ED SUD research.
This study enrolled ED patients eligible to receive buprenorphine to assess program implementation and 30-day treatment engagement. Team training involved webinars to present

study procedures with quizzes, role-plays, observation and feedback, and development of site-specific standard operating procedures to assess staff knowledge. In addition to protocol-specific training, research assistants (RAs) participated in an interactive interviewing training on the collection of sensitive data, interviewer safety, and effective boundary-setting. RAs met weekly with the lead investigative team to discuss implementation, share barriers, and provide feedback.

Conclusions: Effective recruitment and retention strategies were honed through interactive skills training. These included the ability to establish rapport with patients and forge successful partnerships with busy ED staff. RAs with prior experience in the ED helped guide new RAs by providing real-world examples, recommending techniques for engaging patients, providers, nurses and other ED staff, and orienting them to "unwritten" rules of the ED. Training for the next phase of this research will expand on assessing competency via observed practicum—encompassing patient approach, rapport-building, and consenting—to target the intangible skills most salient to recruitment.
Formal inclusion of experienced RAs in study training may be valuable for peer-to-peer coaching. Mock patient visits in the ED are also recommended to increase staff comfort in the fast-paced, high-acuity setting. Skills training on boundary-setting, rapport-building, and safety, in addition to standard protocol training, may build competency in research staff working with SUD populations in the ED.

IMPROVING LINKS FROM EMERGENCY DEPARTMENTS TO COMMUNITY-BASED SERVICES FOR PEOPLE WITH ADDICTION AND MENTAL HEALTH NEEDS – UTILIZATION AND COSTS

*Mary Brolin**[1], Constance Horgan[1], Sharon Reif[1]*

[1]Brandeis University, Heller School for Social Policy and Management

Abstract Detail: Human
Drug Category: Other, substance use (not specified by substance)
Topic: Treatment
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Patients with complex needs often lack access to appropriate healthcare services, resulting in poor health and repeated utilization of high-cost acute services. These challenges are exacerbated for patients with co-occurring substance use disorders (SUD) and mental disorders. The Lahey-Lowell Joint CHART Program was funded from 2016 to 2017 to improve healthcare delivery and reduce health system costs. CHART implemented teams of community health workers led by a social worker to identify high-need patients and provide intensive, community-based case management services. We report here on the impact on hospital and emergency department utilization and costs.
Methods: Analyses used a pre/post design and a comparison group, using patient data for one year prior and two years post implementation, to determine if CHART use of, and costs related to, acute treatment services, and if these effects varied by presence of SUD and/or mental disorders.
Results: Half of patients had co-occurring SUD and mental disorders. Overall, the study demonstrated gross savings of $4.5 million over two years, or $5,122 per person. Savings were

largely attributable to reduced hospitalization spending, generally the costliest type of health care. CHART patients showed some reductions in hospital admissions and days and significant reductions in observation visits compared to treatment-as-usual (TAU) patients. Emergency department use was not significantly reduced compared to TAU. Patients without co-occurring SUD and mental disorders had a significant decrease in hospital admissions and days compared to other patients.
Conclusions: Although per-person savings are modest, savings exceeded implementation costs. Health systems across the country are increasingly prioritizing social factors that affect patient outcomes. By addressing social determinants of health, CHART patients had fewer hospital admissions and shorter stays. Patients with more complex needs, including those with co-occurring SUD and mental disorders, may need additional supports to improve their health and reduce service use.

Late-Breaking Presentation Session II

3:30 p.m. - 4:30 p.m.

A NEW SURGE IN OPIOID-RELATED OVERDOSES IN THE EMERGENCY DEPARTMENT DURING COVID-19

Taylor Ochalek[*1], Kirk Cumpston[1], Brandon Wills[1], Tamas Gal[1], F. Gerard Moeller[1]*
[1]*Virginia Commonwealth University*

Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Substance Use Disorder
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Individuals with opioid use disorder (OUD) may be more susceptible to SARS-COv-2 infection and may also be disproportionately burdened by the health and societal consequences associated with COVID-19, such as increased unemployment rates and worsened mental health symptoms. These pandemic-related costs may place individuals at a heightened likelihood of using illicit opioids and experiencing an opioid-related overdose (OD). Using real-time monitoring, we characterized the amount of unintentional opioid ODs in an urban emergency department (ED) in Richmond, Virginia during COVID-19.
Methods: Data on the number of overdoses from 2019 to April 2020 were obtained from twice daily reports generated by a machine learning algorithm that identifies potential opioid overdoses from patients' electronic medical records based on the following chief complaint terms: “OD,” “overdose,” “opioid,” “heroin,” “fentanyl,” “AMS,” and “altered mental status.” Intentional ODs and non-opioid-related ODs were excluded.
Results: Opioid-related overdoses increased from an average of 6 per month in 2019 to 50 and 57 in March and April 2020, translating to 721% and 836% increases, respectively. OD visits also increased substantially from February to March and April. During COVID-19, there has been a consistently greater frequency of days with OD visits, with at least one OD reported on 74% and 90% of days in March and April compared to only 10% and 24% of days in January and February of this year, respectively. Data from May 2020 and statistical analyses will be available for presentation at the June 2020 meeting.

Conclusions: We have observed an increasing trend of opioid-related OD visits in our local ED during COVID-19 via real-time monitoring. Given this, efforts are needed to examine the effects of the pandemic on the opioid crisis and to improve ED-initiated treatment and public health interventions to reduce the potential downstream effects of COVID-19 on exacerbating the opioid epidemic.

UNDERSTANDING FENTANYL OVERDOSE RISK AMONG PEOPLE WHO USE COCAINE

Jaclyn Hughto[1], Patricia Case[2], Wilson Palacios[3], Sarah Ruiz[4], Brittni Reilly[4], Abigail Tapper[5], Thomas Stopka[6], Traci Green[5]*

[1]Brown School of Public Health, [2]Northeastern University, [3]University of Massachusetts Lowell, [4]Massachusetts Department of Public Health, [5]Brandeis University, [6]Tufts University School of Medicine

Abstract Detail: Human
Drug Category: Polydrug (i.e. Use of more than one drug combination)
Topic: Epidemiology
Abstract Category: Original Research
Designation: M.P.H., Ph.D.

Abstract: Aim: Fatal overdoses involving cocaine and opioids (namely fentanyl) have increased in recent years in Massachusetts. The present study aimed to describe risk factors for fatal overdose among individuals who use cocaine/crack and/or opioids.
Methods: We conducted a multi-site rapid assessment ethnographic study from August 2017 to October 2019 among Massachusetts residents who currently use drugs. This analysis harvested from the 465 individuals surveyed who reported using cocaine and/or opioids in the past month. Descriptive statistics examined differences (X2; $p<0.05$) in overdose risk indicators by drug use.
Results: The majority of the sample (66%) had used cocaine/crack and opioids in the past month (PolyCCOp); 18.9% used only opioids (Op); 9.2% used cocaine/crack but no opioid use history (CC_OpH-); and 6.2% used cocaine/crack with opioid use history (CC_OpH+). The majority of people using opioids currently (64% Op; 69% Poly_CCOp) or in the past (52% CC_OpH+) had overdosed versus 28% of those without an opioid use history (CC_OpH-). The CC_OpH- group had significantly less awareness of fentanyl: 14% had not heard of fentanyl (2% PolyCCOp; 4% CC_OpH+; 4% Op) and 92% did not suspect that fentanyl was in their drugs (42% CC_OpH+; 83% Op; 88% Poly_CCOp). A significantly lower proportion of the CC_OpH- group had a personal naloxone kit (23% vs. 52% CC_OpH-; 56% Op; 71% Poly_CCOp) and less than half (44%) had received naloxone training compared with 69% of CC_OpH-, 73% of Op, and 80% of the Poly_CCOp groups.
Conclusions: Findings suggest that people who primarily use cocaine/crack and have no history of opioid use may be at greatest risk for a fatal overdose as they have less awareness of fentanyl in the drug supply and are less prepared to respond to an overdose than other groups. Public health campaigns are needed to increase fentanyl awareness and overdose prevention preparedness among people primarily using cocaine/crack.

CORRELATES OF NON-PRESCRIBED BUPRENORPHINE USE DURING INCARCERATION AND IN COMMUNITY SETTINGS

Anjalee Sharma[*1], Joshua D. Lee[2], Laura Monico[1], Kristi Dusek[1], Ryan McDonald[2], Mia Malone[2], Angela DeVeaugh-Geiss[3], Howard Chilcoat[3], Jan Gryczynski[1]*

[1]Friends Research Institute, [2]New York University School of Medicine, [3]Indivior, Inc.

Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Substance Use Disorder
Abstract Category: Original Research
Designation: M.S.W.

Abstract: Aim: Buprenorphine is an effective medication for opioid use disorder (OUD), but diversion has been reported in community settings and within the criminal justice system. We sought to examine associations of non-prescribed (i.e., diverted) buprenorphine use in each of these settings.
Methods: A structured interview was conducted with adults with OUD/opioid misuse and recent incarceration experience, recruited in Baltimore, MD and New York, NY (n=150 in each state). Multivariable logistic regression (analytical N= 283) was used to examine associations between having ever used non-prescribed buprenorphine (a) in the community and (b) during incarceration; and participant characteristics (recruitment state, age, sex, race, housing situation, marital status, lifetime years incarcerated, prior methadone and buprenorphine treatment, and age of first opioid misuse).
Results: The sample was 82% male, 53% black, with a mean (SD) age of 42 (10) years. Overall, 74.9% of participants endorsed lifetime use of non-prescribed buprenorphine (19.4% community only, 8.5% incarceration only, 47.0% both settings). Use of non-prescribed buprenorphine during incarceration was significantly associated with younger age (Adjusted Odds Ratio [AOR]=0.96 [95% Confidence Interval=0.93, 0.99]; p=0.006) and total lifetime years of incarceration (AOR=1.09 [1.05, 1.13]; p<0.001). Use of non-prescribed buprenorphine in the community was significantly associated with Maryland recruitment site (AOR=3.92 [1.69, 9.10]; p=0.001), not being married (AOR=4.02 [1.78, 9.11; p<0.001), and lifetime buprenorphine treatment (AOR=3.10 [1.63, 5.90]; p<0.001). Additionally, compared to living in temporary housing (e.g., halfway or recovery house), non-prescribed buprenorphine use was associated with stable (AOR=2.25 [1.04, 4.88]; p=0.04) or unstable (i.e., homeless or shelter) housing (AOR=3.77 [1.55, 9.15]; p=0.003).
Conclusions: This study found some overlapping, as well as distinct, participant characteristics that were associated with use of non-prescribed buprenorphine during incarceration and in the community. These findings illustrate the complexities of buprenorphine diversion, which may manifest differently based on community and incarceration contexts.

DEEP BRAIN STIMULATION OF THE NUCLEUS ACCUMBENS/VENTRAL CAPSULE FOR CO-OCCURRING OPIOID AND BENZODIAZEPINE USE DISORDER

James Mahoney[*1], Marc Haut[1], Sally Hodder[1], Wanhong Zheng[1], Laura Lander[1], James Berry[1], Nicholas Brandmeier[1], Manish Ranjan[1], Victor Finomore[1], Gene-Jack Wang[2], Dardo Tomasi[3], Ehsan Shokri Kojori[3], Ali Rezai[1]*

[1]West Virginia University School of Medicine, [2]National Institute on Alcohol Abuse and Alcoholism, [3]National Institute of Drug Abuse, National Institutes of Health

Abstract Detail: Human
Drug Category: Polydrug (i.e. Use of more than one drug combination)
Topic: Other
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: To evaluate the safety, tolerability, and feasibility of deep brain stimulation (DBS) of the Nucleus Accumbens/Ventral Capsule (NAc/VC) in a 33-year-old man with treatment refractory opioid and benzodiazepine use disorder. Secondary aims included evaluating the effects of DBS on substance use, substance craving, and frontal/executive functions.
Methods: Following eligibility determination, DBS electrodes were implanted bilaterally within the NAc/VC. After surgical recovery, titration of DBS stimulation parameters were made, with optimized adjustment performed during outpatient week 7. Outcome measures included assessments of substance use (qualitative and quantitative urine toxicology), substance craving, and frontal/executive functions using the balloon analogue risk task (BART) and brain metabolism by FDG PET.
Results: During the 12-week outpatient follow-up assessment (114 days post-DBS implantation), DBS of the NAc/VC was found to be safe and well tolerated. The subject remained entirely abstinent from illicit substance use and fully engaged in comprehensive addiction treatment. In comparison to baseline, pre-DBS craving ratings (assessed via 0-100 visual analog scale; 0 = no craving and 100 = maximum craving), post-DBS reductions were noted in opioid and benzodiazepine cravings. The most substantial reduction was in benzodiazepine craving following the final setting adjustment (mean craving across weeks 8-12: 1.0+2.2) in comparison to baseline craving (53.4+29.5). Performance on the BART was most improved following the final adjustment (217.7+76.2) in comparison to baseline performances (131.3+28.1). At the 12-week endpoint, PET findings demonstrated an increase in FDG in the dorsolateral prefrontal and medial premotor cortices and decreases in the basal ganglia, thalamus, and cerebellum.
Conclusions: In this subject with treatment refractory opioid and benzodiazepine use disorder, DBS of the NAc/VC was safe and well-tolerated, reduced substance use and craving, and improved frontal/executive functions/metabolism. While promising, DBS of the NAc/VC requires further study to establish safety followed by replication in a controlled trial to determine the impact on substance use.

ACCEPTABILITY OF A GAMIFIED OPIOID MISUSE PREVENTION INTERVENTION FOR TEENS

Alison Oliveto[1], Patricia Wright[1], Nihit Kumar[1], Srinivasa Gokarakonda[1], Ian Fischer-Laycock[1], Ronald Thompson[1]*

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Prevention

Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: This study assessed initial acceptability of a gamified opioid misuse (OM) prevention intervention (SafeUse) for delivery via smartphone among teenage students.
Methods: Phase I: Evidence-based educational and refusal skills training materials developed/disseminated by the National Council on Patient Information and Education (e.g., BeMedWise) and the National Institute on Drug Abuse were adapted and applied to clinically- and scientifically-informed situations in which opioids are typically introduced to youth using standard product development methods to create the SafeUse prototype game app. SafeUse is a gamified opioid misuse prevention intervention for teens that simulates real-life scenarios and provides players with decision points followed by consequences for each decision. The modules change depending on the player's choices and provide information about opioids throughout each scenario. Phase II: Nine 8th grade students (mean age=13.4 years; 66.7% female; 55.6% white/44.4% black/11.1% Hispanic) were enrolled into a mixed methods study and completed assessments about perceptions of opioids and/or gaming components prior to and following access to SafeUse. After one week of playing SafeUse, participants provided feedback in a 60-90-minute focus group on its acceptability, relevance, understandability, and needs for design and content improvement.
Results: Qualitative analyses of focus groups are ongoing. Participant self-reports indicated that: they liked SafeUse (100%); SafeUse increased knowledge of prescription opioids (PO; 100%); content increased confidence to refuse a PO from peers (100%); they liked SafeUse avatars (100%); situations were realistic (100%); language level was appropriate (100%), they would play another game module (100%); liked how the game looked on smartphone (89%); liked playing through every decision option (100%); liked the voice acting (78%), and the game was fun (100%).
Conclusions: Initial findings suggest that SafeUse is acceptable and likely educational to teenagers and worthy of further research.

THE ROLE OF G-PROTEIN BIAS IN ANTI-NOCICEPTIVE POTENCY AND TOLERANCE; ANALYSIS OF THE G-PROTEIN BIASED MU OPIOID RECEPTOR AGONISTS KURKINOL AND KURKINORIN

Amy Alder[*1], Dan Luo[2], Thomas Prisinzano[2], Bronwyn Kivell[1]*
[1]Victoria University of Wellington, [2]University of Kentucky

Abstract Detail: Animal Study
Drug Category: Opiates/Opioids
Topic: Behavior
Abstract Category: Original Research
Designation: B.Sc.

Abstract: Aim: Prescription opioids are highly addictive compounds that act as gateway drugs for further illicit drug use. The addictive nature of these compounds, the worsening opioid crisis worldwide, and the development of analgesic tolerance has led to a great need for non-addictive efficacious opioids. Biasing signaling towards the G-protein pathway over the β-arrestin pathway at the mu-opioid receptor (MOR) is theorized to reduce the tolerant properties of

opioids while maintaining potent analgesic effects. We aim to characterize the anti-nociceptive and tolerant effects of two compounds in vivo.
Methods: In this study, the anti-nociceptive and tolerant effects of two novel MOR agonists, kurkinorin (bias = 0.34) and kurkinol (bias = 0.14), with limited abuse liability were assessed in the hot-water dose response tail-flick assay of acute anti-nociception and chemotherapy-induced neuropathic model (CINP) of chronic pain in C57 Bl/6 (n=72) and β-arrestin knockout mice (β-arr-/-) (Wt n= 18, β-arr-/- n = 18).
Results: We found that the degree of bias correlated to potency and tolerance in the hot water tail-flick assay in wildtype (Wt) mice. In β-arr-/- mice, morphine showed marked improvements in potency (β-arr-/-; ED50=5.02 mg/kg, Wt; ED50=7.0 mg/kg) and tolerance (β-arr-/-; ED50=9.1 mg/kg, Wt; ED50=13.5 mg/kg), while kurkinorin had reduced anti-nociceptive tolerance (β-arr-/-; ED50=6.0 mg/kg, Wt; ED50=10.7 mg/kg). Kurkinol showed no difference compared to wildtype controls. In the chemotherapy-induced neuropathic pain model, the strongly G-protein bias kurkinol (mechanical; ED50=1.5 mg/kg, cold; ED50=1.9 mg/kg) was more potent than kurkinorin (mechanical; ED50=9.1 mg/kg, cold; ED50= 11.6 mg/kg) and morphine (mechanical; ED50=9.2 mg/kg, cold; ED50= 10.5 mg/kg). However, there was no improvement in tolerance to mechanical and cold allodynia.
Conclusions: These results indicate that biased agonism may not provide improved tolerance in chronic pain states, which could lead to an increase in doses to maintain sufficient analgesia and the risk of dependence and addiction.

ETHANOL PRE-EXPOSURE DIFFERENTIALLY IMPACTS THE REWARDING AND AVERSIVE EFFECTS OF α-PYRROLIDINOPENTIOPHENONE (α-PVP): IMPLICATIONS FOR DRUG USE AND ABUSE

Katharine Nelson[*1], Hayley Manke[1], Jacob Bailey[1], Anna Vlachos[1], Karina Maradiaga[1], Tania Weiss[1], Shihui Huang[1], Kenner Rice[2], Anthony Riley[1]*

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Abstract Detail: Animal Study
Drug Category: Polydrug (i.e. Use of more than one drug combination)
Topic: Behavior
Abstract Category: Original Research
Designation: M.A.
Abstract: Aim: To assess the impact of ethanol (EtOH) history on the rewarding (conditioned place preferences) and aversive (conditioned taste avoidance, hyperthermia and hyperactivity) effects of α-PVP.
Methods: Adult male Sprague-Dawley rats (n = 48) were intraperitoneally (IP) injected with EtOH (2 g/kg) or saline every 3rd day for five exposures. Following pre-exposure, a combined taste avoidance/place preference procedure was initiated in which a saccharin solution was given followed by an injection of various doses of α-PVP (1.5, 3 or 5 mg/kg, IP) or vehicle (n=6/group) and then placement on one side of the CPP apparatus for 30 min. On the following day, rats were given water, injected with saline and placed on the opposite side of the apparatus. This cycle was repeated three times followed by a final assessment of side preference. Following drug washout, subjects were randomly injected with various doses of α-PVP monitored for temperature by subcutaneous probes for 8 hours. Following another washout, subjects were injected with α-PVP or vehicle and motor activity was monitored for 1 hour. Mixed model ANOVAs were used for each assessment.

Results: Relative to vehicle pre-exposure, ethanol attenuated α-PVP-induced aversions (all ps ≤ 0.04). α-PVP induced place preferences (all ps ≤ 0.042) that were not dependent on pre-exposure. α-PVP produced dose- and time-dependent increases in temperature (all ps ≤ 0.038) with no effect of pre-exposure. α-PVP produced an increase in locomotor behavior that was dose-, time- and pre-exposure-dependent (all ps ≤ 0.027). Significant dose- and time-dependent stereotypies were also produced (all ps < 0.000) with no effect of pre-exposure.
Conclusions: Ethanol pre-exposure attenuated several of the aversive effects of α-PVP but had no impact on α-PVP's rewarding effect. Given that the balance of aversion and reward affect drug acceptability, these results suggest that ethanol history may increase α-PVP's abuse potential.

EXPLORATION OF VALUES AND THE IMPACT OF CHRONIC PAIN AND OPIOID USE

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Treatment
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Values-based approaches to therapy are increasingly used for chronic pain patients who rely upon opioid therapy for pain management. We do not yet understand how chronic pain and opioid use may differentially impact value domains such as family, friends, or work. The aim of this study is to characterize the ways in which chronic pain and values interact to inform therapy approaches for this population.
Methods: Participants experiencing chronic musculoskeletal pain for 3+ months and taking a prescription opioid (N=327) completed a self-report survey with questions asking about importance of different values in six areas of life (i.e. family, intimate relationships, friendship, work, health, growth). We also asked about pain interference with and without opioids, and bothersomeness of pain within each value area. Most participants were white, female, average age 46, who had experienced chronic pain and taken opioids for over one year.
Results: There were significant differences between the six value-areas in importance ratings. Pain interference also differed among the values with the most reported pain interference occurring in work and health areas; though without opioids, work, health, and family each were higher than the other values. Uniformly, for each of the six value areas, pain interference was rated significantly less with than without opioids. The only significant difference between values in the effect of opioid use on pain interference was between family and health, where the effect for family was greater than for health.
Conclusions: Results indicate that people perceive opioids as helping reduce pain interference related to participation in various activities aligned with their values. Finding alternative ways to help patients engage in valued activities (particularly family activities) may help patients learn to be less reliant upon opioids.

Oral Communications III, Q&A

Abuse Potential

3:30 p.m. - 4:30 p.m.

EVALUATION OF SEDATIVE-MOTOR AND REINFORCING EFFECTS OF A NOVEL BIOISOSTERE IMIDAZODIAZEPINE IN RHESUS MONKEYS

James Rowlett[*1], Tanya Pareek[1], Jemma Cook[1], Daniela Rüedi-Bettschen[1], Lalit Golani[2], Daniel Knutson[2], Farjana Rashid[2], Lais Berro[1], Donna Platt[1], James Cook[2]*

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Abstract Detail: Animal Study
Drug Category: Sedative-Hypnotics
Topic: Behavior
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Bioisosteric imidazodiazepine analogs have shown preclinical efficacy as novel anti-epileptic compounds. In this study we evaluated the sedative-motor effects and abuse potential of a key analog in this series, KRM-II-81.
Methods: The observable behavioral (n=4) and reinforcing (n=2) effects of i.v. KRM-II-81 were evaluated in female rhesus monkeys. Drug-associated behavior (e.g., sedative effects, observable ataxia), as well as species-typical behavior (e.g., self-groom) were determined using the procedures of Duke et al. (2018, JPET 366: 145-57). Reinforcing effects were assessed under a progressive-ratio schedule of midazolam reinforcement and compared with the standard benzodiazepine, alprazolam. Repeated-measures ANOVAs and Dunnett's post-hoc tests were used to determine which doses were significantly different from the vehicle.
Results: In the observable behavior procedure, only the mildest form of sedation ("rest/sleep posture") was induced by KRM-II-81 (doses of 10 and 17 mg/kg, i.v., $p<0.05$). Tactile/oral exploration and self-groom were both significantly attenuated at the highest dose tested ($p's<0.05$). In self-administration, alprazolam was self-administered above vehicle levels in both monkeys. In contrast, KRM-II-81 was self-administered above vehicle levels in one monkey, but not in a second monkey over a 30-fold dose range.
Conclusions: KRM-II-81 engendered only mild sedative effects and suppressed species-typical behavior only at the highest doses tested, consistent with this compound being an □2/3 subunit-preferring GABAA positive modulator. Importantly, our ongoing studies suggest this compound may have lower abuse potential than the conventional benzodiazepine, alprazolam.

RELATIVE POTENCY OF INTRAVENOUS OXYMORPHONE COMPARED TO OTHER MU-OPIOID AGONISTS IN HUMANS

Shanna Babalonis[*1], Sandra D. Comer[2], Jermaine D. Jones[2], Paul A. Nuzzo[1], Michelle R. Lofwall[1], Jeanne Manubay[2], Kevin Hatton[1], Robert Whittington[3], Sharon L. Walsh[1]*

[1]University of Kentucky, College of Medicine, [2]Columbia University Irving Medical Center/NY State Psychiatric Institute, [3]Columbia University Vagelos College of Physicians and Surgeons

Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Other
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Oral formulations of the mu-opioid analgesic, oxymorphone, were approved in the U.S. in 2006. Since this time, misuse of oxymorphone, particularly through the intravenous (IV) route, has caused significant public health harms; however, no controlled data on its IV abuse potential are available. The primary aim of this study was to examine the relative potency of IV oxymorphone compared to IV oxycodone, morphine and hydromorphone on pharmacodynamic outcomes in order to select doses for a subsequent fully randomized study of abuse liability and self-administration.
Methods: Participants (n=6) with opioid use disorder, physical dependence and current IV use completed this two-site, within-subject, double-blind, placebo-controlled, inpatient study. During each session, one IV dose was administered (mg/70 kg): oxymorphone (1.8, 3.2, 5.6, 10, 18, 32, 56), hydromorphone (1.8, 3.2, 5.6, 10, 18), oxycodone (18, 32, 56), morphine (18, 32, 56) and placebo. Doses of each drug were administered in ascending order for safety but were otherwise randomized. Data were collected prior to and 6 hrs. post-dose. Primary outcomes included safety/physiological outcomes (O2 saturation, end tidal CO2, respiration rate) and subjective measures of drug liking.
Results: All of the drugs tested produced prototypical, dose-related opioid effects (e.g., miosis, increased EtCO2). Oxymorphone was more potent than the comparator opioids on several measures, including respiratory depression and subjective drug liking ($p<.05$). In general, oxymorphone doses ≥5.6 mg/70 kg produced greater peak ratings of drug liking than all other comparator doses; oxymorphone ≥18 mg/70 kg produced greater respiratory depression than all other conditions.
Conclusions: Despite the relatively small sample size, this completed study detected robust oxymorphone effects and demonstrated that oxymorphone is far more potent than previously reported. Overall, these data align with recent surveillance reports indicating that, after adjusting for prescription rates/availability, oxymorphone was injected at the highest rates, relative to other prescription opioids.

LORCASERIN DOSE-DEPENDENTLY SUPPRESSES OXYCODONE INTAKE BY INCREASING DEMAND ELASTICITY IN MALE SPRAGUE-DAWLEY RATS

Erik Garcia[*1], Christina Merritt[1], Robert Fox[1], Noelle Anastasio[1], Kathryn Cunningham[1]*
[1]University of Texas Medical Branch

Abstract Detail: Animal Study
Drug Category: Opiates/Opioids
Topic: Substance Use Disorder
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: The serotonin (5-HT) 2C receptor (5-HT2CR) is a therapeutic target to control the consumption and appetitive responding for abused drugs including prescription opioids. The FDA-approved 5-HT2CR agonist lorcaserin was employed to test the hypothesis that 5-

HT2CR transmission regulates oxycodone self-administration (SA). The efficacy of lorcaserin to suppress oxycodone intake and the motivation to consume oxycodone was tested using the within-session threshold procedure for oxycodone SA.
Methods: Freely-fed male Sprague-Dawley rats were trained to self-administer oxycodone (0.1 mg/kg/inf) on a fixed ratio 1 (FR1) schedule of reinforcement for 7 days. Then rats began training on the within-session threshold procedure until stable. The within-session threshold procedure systematically increased the price of oxycodone (responses/mg) every 20 min. Rats were allowed to consume/SA oxycodone freely without timeouts during each 20 min. epoch. The total session length was 220 min. Lorcaserin (0.25, 0.5, and 1 mg/kg; i.p.) or saline was injected 20 min. prior to the start of the oxycodone within-session threshold SA sessions.
Results: The effects of price increases on oxycodone SA was determined using exponentiated behavioral economic demand analysis. Lorcaserin (1 mg/kg) dose-dependently suppressed oxycodone intake when the price of oxycodone was low, and lorcaserin increased demand elasticity, suggesting that lorcaserin decreased the motivation for oxycodone as evidenced by a rapid reduction of oxycodone consumption as the price increased. This effect was mediated by action at 5-HT2CR because the effects of lorcaserin were reversed by pretreatment with SB242084 (0.5 mg/kg; i.p.), a 5-HT2CR antagonist.
Conclusions: Demand elasticity estimates the motivational efficacy of a reinforcer and is independent of consumption at low-unit prices. Therefore, the 5-HT2CR is a novel therapeutic target to suppress the reinforcing effects of oxycodone by reducing its 'essential value'. We are currently testing the ability for lorcaserin to suppress the acquisition of oxycodone SA and evaluating the abuse potential of lorcaserin alone.

Endocarditis

ESTIMATING THE LONG-TERM INCIDENCE OF AND MORTALITY FROM SEVERE BACTERIAL INFECTIONS AND OVERDOSE RELATED TO INJECTION OPIOID USE: A MODELING STUDY

Joshua Barocas[*1], Golnaz Eftekhari Yazdi[1], Alexandra Savinkina[1], Shayla Nolen[2], Caroline Savitzky[1], Honora Englander[3], Jeffrey Samet[4], Benjamin Linas[4]*

[1]Boston Medical Center, [2]Brown University School of Public Health, [3]Oregon Health Sciences University, [4]Boston University School of Medicine

Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Epidemiology
Abstract Category: Original Research
Designation: M.D.

Abstract: Aim: Bacterial infections are common complications in persons who inject opioids (PWIO) associated with significant morbidity, mortality, and cost. In the context of an opioid epidemic, tools are needed to estimate incidence and burden of disease. We aimed to project long-term incidence, outcomes, and fraction of all-cause mortality attributable to injection-related endocarditis (IE), skin and soft tissue infections (SSTI), and overdose among PWIO in the U.S.

Methods: We developed a microsimulation model that simulates the natural history of injection opioid using injection frequency and practices as the framework to forecast injection-related outcomes. Simulated individuals progress through a series of modules in which they acquire infections and encounter interventions, which can change injection behaviors and alter risk of future sequelae. We used literature and primary data for model parameters. We varied parameter values to fit the simulation to 1-year IE and fatal overdose incidence, 3-year IE mortality, and life expectancy among PWIO. We simulated 10-year incidence of and mortality attributable to infections and overdose. We estimated future burden of IE death by multiplying the projected mortality rate by the estimated number of PWIO.
Results: We matched 1-year IE (55 vs 52 per 10,000; standard error [SE] 5.8%), 1-year fatal overdose (68 vs 70 per 10,000; SE 0.74%), 3-year IE mortality (29% vs 35%; SE 17.4%), and remaining life expectancy (35.3 years vs 35.5 years; SE 0.62%). Predicted 10-year incidence of IE, SSTI, and overdose was 716, 3,460, and 3,580 per 10,000, respectively. Attributable fraction of 10-year mortality for IE, SSTI, overdose, and causes unrelated to drug use was 20%, 9%, 32%, and 31%, respectively. Applying model projections to the US PWIO population,198,600 deaths are expected from IE in the next 10 years.
Conclusions: Given current trends, IE and SSTI will account for nearly one-third of all deaths among PWIO in the next 10 years.

NATURAL LANGUAGE PROCESSING TO IDENTIFY PEOPLE WHO INJECT DRUGS IN ELECTRONIC HEALTH RECORDS

David Goodman-Meza[*1], Steve Shoptaw[1], Sergio M. Delgado[1], Raphael J. Landovitz[1], Alex A.T. Bui[1]*

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Abstract Detail: Human
Drug Category: Polydrug (i.e. Use of more than one drug combination)
Topic: Technology Issues
Abstract Category: Original Research
Designation: M.D.

Abstract: Aim: People who inject drugs (PWID) are frequently admitted to hospitals due to infections like infective endocarditis. Accurately identifying PWID in electronic health records (EHR) is important for administrative, surveillance, and research purposes. However, no standard codes (e.g., International Classification of Diseases [ICD]-9/10) exist to characterize these individuals. Our aim was to evaluate the diagnostic accuracy of natural language processing (NLP) with unstructured chart notes compared to an ICD-based algorithm to define a phenotype of PWID in EHR data.
Methods: Cases of endocarditis from 2013-2018 were extracted from UCLA's EHR. Admission notes were reviewed and classified by a human annotator as describing PWID or non-PWID. Word embeddings (Word2Vec) and term frequency–inverse document frequency (TF-IDF) were used for feature extraction. Machine learning models (logistic regression (LR), K-nearest neighbor (KNN), support vector machines (SVM), naïve Bayes, gradient boosted, random forest (RF), and decision trees) were trained on the note classifications. The dataset was split 70% for training and 30% for testing. The ICD-based algorithm was computed based on ICD codes for substance use disorders, HIV, hepatitis C, and homelessness. Receiver

operating curves were plotted and the area under the curve (AUC) for each model was determined.
Results: The dataset was composed of 129 unique admissions; 91 cases were classified as non-PWID, and 38 cases as PWID. The best performing models using Word2Vec were LR (AUC 0.73), SVM (AUC 0.67), and RF (AUC 0.60). In comparison, the best models using TF-IDF were LR (AUC 0.87), SVC (AUC 0.83), and KNN (AUC 0.82). The ICD-based algorithm had an AUC of 0.64.
Conclusions: TF-IDF with LR outperformed other models in diagnostic accuracy for classifying admission notes as pertaining to PWID or not. Future studies using larger datasets may provide better model training that could lead to a more accurate tool to classify cases of PWID in EHR data.

DISCHARGE AGAINST MEDICAL ADVICE AMONG PATIENTS WITH INJECTION AND NON-INJECTION DRUG ASSOCIATED ENDOCARDITIS: A NATIONWIDE STUDY

Simeon Kimmel[*1], June-Ho Kim[2], Bindu Kalesan[1], Jeffrey Samet[1], Alexander Walley[1], Marc Larochelle[1]*

[1]Boston University School of Medicine, [2]Brigham and Women's Hospital

Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Substance Use Disorder
Abstract Category: Original Research
Designation: M.D.

Abstract: Aim: Hospitalizations for injection drug use associated infective endocarditis (IDU-IE) are increasing and discharges against medical advice (AMA) are common. Examining a nationally representative sample, we report trends, risk factors, and timing of AMA discharges for IDU-IE and differences from non-IDU-IE.
Methods: We identified individuals 18-64 with International Classification of Diseases, 9th Revision diagnosis codes for endocarditis in the National Inpatient Sample, a representative sample of United States inpatient hospitalizations from January 2010 to September 2015. We examined unadjusted trends for AMA discharges and used logistic regression to identify factors associated with AMA discharge among all endocarditis, IDU-IE and non-IDU-IE. We also determined the proportion of AMA and non-AMA, live discharges by hospital day.
Results: We identified 7,303 hospitalizations for IDU-IE and 23,811 for non-IDU-IE representing 36,358 national IDU-IE and 118,384 non-IDU admissions, respectively. During this period, AMA discharges for IDU-IE increased from 11.0% to 20.6% and non-IDU-IE from 2.0% to 2.8%. In adjusted models, IDU status was associated with increased odds of AMA discharge [Adjusted Odds Ratio (AOR) 4.34 (95% CI: 3.80-4.95)]. Odds of AMA discharge increased 14% per year for IDU-IE [(AOR 1.14 (95% CI: 1.08-1.20)] and 7% per year for non-IDU-IE [(AOR 1.07 (95% CI: 1.01-1.13)]. Women with IDU-IE had increased odds [AOR 1.2 (95% CI 1.03-1.39)] while those with non-IDU-IE had decreased odds of AMA discharge [AOR 0.68 (95% CI 0.55-0.83)]. Younger age and residing in lower zip code income quartiles had increased odds in all groups. AMA discharges occurred during hospital day 0 to 2 in 32.5 % of IDU-IE and 31.3% of non-IDU IE.

Conclusions: AMA discharges for both IDU-IE and non-IDE-IE have risen but were more common and increased more sharply among those who inject drugs, potentially related to untreated opioid withdrawal. Efforts to prevent AMA discharge are needed, especially early in hospitalizations.

ENDOCARDITIS IN THE MAKING? HIGH PREVALENCE OF BACTERIAL INFECTIONS AND OTHER INJECTION-RELATED COMPLICATIONS AMONG HCV NEGATIVE YOUNG OPIOID INJECTORS

Pedro Mateu-Gelabert[*1], Honoria Guarino[2], Benjamin Eckhardt[3], Ramona Almenana[2], Elizabeth Goodbody[2], Carli Salvati[2]*

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Epidemiology
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Prevention efforts among opioid injectors have focused on viral infections often to the detriment of other medical complications. In this study, we describe the prevalence of bacterial infections and other complications associated with drug injection among young opioid injectors.
Methods: As part of an ongoing RCT to prevent HCV among young opioid users in New York City, we recruited 151 participants. The baseline questionnaire included sociodemographics, injection risk behaviors and history of injection-related complications. Eligibility criteria included: age 18-29; current opioid use (verified by urine drug screening); injecting at least once in past 6 months (self-reported); and HCV and HIV antibody negative (tested on-site).
Results: Participants (mean age = 25) first injected drugs at the mean age of 20.5 (SD: 3.3). 29% were female; 32% Latinx, 64% White, 11% multiracial, and 9% Black. 34% were currently homeless and 86% met criteria for severe OUD. In the last 3 months, participants reported: serious bruising at injection sites (42%); abscesses (14%); swelling at injection sites (52%); scarring at injection sites (64%); cotton fever (17%); collapsed veins (15%); swelling of hands or forearms (28%); swelling of feet or legs (10%); blood clots (3%); and cellulitis (2%). On a 1-10 scale, 10 being best, 23% of participants rated the health of their veins as <5. 52% reported rotating injection sites often or very often.
Conclusions: Despite their HIV/HCV negative status and efforts to rotate injection sites, young opioid injectors report a high prevalence of bacterial infections and other drug injection-related complications. Drug treatment and harm reduction programs urgently need to include basic education about safer injection practices that can prevent bacterial infections.

HIV/HCV/Stigma

COMBATTING STIGMA IN RURAL SUBSTANCE USE SERVICES FOR PEOPLE WHO INJECT STIMULANTS

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Abstract Detail: Human
Drug Category: Stimulants
Topic: Policy
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Limited access to healthcare, substance use treatment and prevention services, and harm reduction programming contributes to increased morbidity and mortality in rural communities facing epidemic levels of substance use. Factors associated with utilization of a rural harm reduction program designed for people who inject drugs (PWID) were examined to understand barriers to uptake.
Methods: Syringe service program (SSP) uptake was assessed in three counties varying in urban-rural status in Appalachian Kentucky. Knox County is entirely non-metropolitan and the focus of the present analysis. Eligible participants reported having injected substances non-medically in the month prior to interview and were at least 18. Participants were recruited using Respondent-Driven Sampling (RDS) and completed structured interviews between May 2018 and September 2019 (n=131).
Results: Mean age of the sample was 37.4, 58.8% were female. Primary drugs of injection were methamphetamine (57.3%), non-prescribed buprenorphine (26%), and non-prescribed opioids (11.5%). 41.2% reported being HCV+; 2.3% were HIV+. 61 reported using the SSP (46.6%). Non-SSP users were more likely to report current employment (p=.04), and reported fewer injections per day (p=.01). Nevertheless, sharing behaviors were elevated in the non-SSP sample: 18.3% shared needles with 2+ people in past 3 months, compared with 9.3% of SSP users (p=.024). Among the non-SSP sample, the primary sources of injection equipment were: street purchase (30%), friend (25.7%), pharmacy (18.6%), someone who goes to the SSP (18.6%), and drug dealers (18.6%). The major barrier to attendance was fear/stigma (45.7%).
Conclusions: Rural harm reduction programs are increasingly being implemented to reduce disease transmission risk and adverse medical consequences of injection drug use in populations that are vulnerable to HIV acquisition. Combatting stigma in rural communities is critically important for improving uptake of these emerging public health programs and supporting healthier behaviors.

TESTING FOR REINFECTION IN PATIENTS CURED OF HEPATITIS C INFECTION WITH DIRECT ACTING ANTIVIRALS AT A MULTIDISCIPLINARY ADDICTION TREATMENT PROGRAM

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Other
Abstract Category: Original Research

Designation: M.D., M.P.H.

Abstract: Aim: Treatment of chronic hepatitis C infection (HCV) is encouraged in all patients regardless of whether substance use is present. Guidelines recommend follow up HCV viral load testing (FVLT) at least annually in patients with substance use disorder after successful treatment of HCV with direct-acting antivirals (DAA). There is little evidence describing use of FVLT in real world settings. We aimed to identify patterns of FVLT among patients treated for HCV with DAAs in a primary care clinic within a multi-disciplinary addiction treatment program.
Methods: We reviewed medical records of all adult patients who were cured of HCV infection with DAAs between 2015 and 2018 at a multi-disciplinary addiction treatment program. The primary outcome was presence of FVLT after cure. Information on demographics and addiction treatment was gathered.
Results: Among 135 total patients for whom complete data was available, the mean age was 46.3 years, 71.1% were male, and 76.3%, 13.3%, and 10.4% were White, Hispanic, and Black, respectively. A total of 81 patients (60%) were offered FVLT. Among those who were offered FVLT, 2.5% opted out, and viral load was negative in 93.8% and positive in 3.7%. The average interval between cure of HCV infection and FVLT was 26.6 months. Among 54 patients (40%) who were not offered FVLT, 74.1% were lost to follow up after HCV cure. Among those offered FVLT, 66.7% received methadone, 21% received buprenorphine, and 12.3% received non-pharmacological forms of addiction treatment.
Conclusions: The majority of patients were offered FVLT as recommended by guidelines and 93.8% of those offered testing remained free of HCV infection. Barriers to providing follow up HCV testing include loss to follow up. Interventions to increase use of follow up HCV viral load testing are needed.

ROLE OF THE PVTA- ACCUMBENS NEUROCIRCUITRY IN CONCURRENT CHOICE OF SUCROSE AND COCAINE IN FEMALE F344/N AND HIV-1 TG RATS

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Abstract Detail: Animal Study
Drug Category: Stimulants
Topic: HIV/Immune
Abstract Category: Original Research
Designation: M.A.

Abstract: Aim: The fronto-striatal system mediating motivational features of goal-directed behavior is damaged by HIV-1, possibly contributing to apathy observed in 30-60% of HIV-1 patients. HIV-1 transgenic (Tg) rats are used to model HIV-1 protein exposure in individuals under viral suppression and have been shown to exhibit attenuated sucrose- and cocaine-maintained responding and deficits in concurrent choice relative to controls. The present experiment used DREADDs in female F344/N (n=20) and HIV-1 Tg (n=20) rats to determine if stimulating hM3D(Gq) receptors on ventral tegmental area cells projecting to the accumbens will resolve HIV-induced deficits in choice behavior.

Methods: Rats first lever-pressed for sucrose (5% w/v) and then cocaine (0.2/0.75 mg/kg/inf) using fixed- and progressive ratio (PR) schedules. Concurrent choice between sucrose and cocaine was then tested in DREADDs (n=24) and sham (n=16) rats over 7 days and following IV C21. Within F344/N and HIV-1 groups, RMANOVAs determined effects of surgery (DREADDs and sham), and within-subjects factors including testing day, type of reward, C21 dose (0.01, 0.03, 0.10, 0.30mg/kg/inf), and time within sessions.
Results: Compared to F344/N, HIV-1 Tg rats exhibited attenuated acquisition of sucrose responding ($F(1,105)=135.2$, $p\leq0.001$), but not escalation of PR cocaine responding. F344/N females initially chose sucrose (39.4±6.5) over cocaine (24.6±6.5), but, after 7 sessions, chose cocaine (58.1±8.7) over sucrose (34.8±7.9). 0.03mg/kg IV C21 decreased sucrose responding in F344/N DREADDs animals so that cocaine was chosen over sucrose compared to sham animals who chose sucrose over cocaine ($F(1,14)=4.702$, $p\leq0.05$). HIV-1 Tg females earned equal sucrose (Day1:17.5±7.4; Day7:40.4±9.9) and cocaine (Day1:16.2±7.4; Day7:40.6±8.1) rewards and IV C21 did not significantly alter choice compared to sham animals.
Conclusions: The finding that choice behavior was modulated by stimulation of DREADDs in F344/N but not HIV-1 Tg animals indicates the VTA-NAc circuit should be a therapeutic target of interest when developing treatments to resolve HIV-1-induced deficits in goal-directed behavior.

GREATER MOTOR DEFICITS AND ABNORMALLY LOWER GLOBUS PALLIDUS FRACTIONAL ANISOTROPY IN HIV+ WOMEN THAN IN HIV+ MEN

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Abstract Detail: Human
Drug Category: Other, HIV and Sex
Topic: Imaging
Abstract Category: Original Research
Designation: D.Phil.

Abstract: Aim: Several studies of HIV-positive (HIV+) individuals found higher prevalence of cognitive impairment in women than in men. However, whether sex-specific differences on brain white matter (WM) microstructure exist in HIV+ individuals is unknown and was evaluated in this study.
Methods: 38 HIV+ (20 men, 18 women) and 47 seronegative (SN) (20 men, 27 women) participants were assessed with brain MRI, including diffusion tensor imaging (DTI), and cognitive assessments (7 neuropsychological domains). Fractional anisotropy (FA) and mean diffusivity (MD) were measured in 6 regions of interest (ROIs): corpus callosum (CC), coronae radiate (CR), internal capsule (IC), uncinate fasiculi (UNC), basal ganglia and thalamus. Group comparisons were made with linear mixed effects model, with sub-regions and hemisphere (left/right) as repeated factors for each ROI.
Results: HIV+women, but not men, were slower than sex-matched controls on Motor function (HIV*Sex interaction: p-dominant=0.007, p-non-dominant=0.039). Similarly, only HIV+women but not men had lower FA in the globus pallidus (GP, interaction-p=0.011) and CC-genu (interaction-p=0.092) than same-sex SN-controls. Additionally, regardless of sex, the HIV+ group had poorer Executive Function, Speed, and Attention than SN-controls (p=0.001-

0.008), as well as lower FA and higher MD in multiple brain regions (p=<0.001-0.044). Across all participants, Attention correlated with UNC-FA (p<0.001, r=0.5) and CC-FA (p=0.03, r=0.2), while Speed correlated with CC-FA (p=0.012, r=0.27). Furthermore, slower dominant-hand motor function was generally associated with lower UNC-FA, except for HIV+women (Sex*HIV*UNC-FA: p=0.074).
Conclusions: Sex-specific alterations were found on both cognitive function and microstructural (DTI) measures in HIV+ individuals. The abnormally lower FA in GP and CC-genu suggests lesser neuronal integrity in these brain structures in HIV+women, but not HIV+men. Likewise, the greater motor deficit in HIV+women than in HIV+men suggests sex-specific effect on the motor network. However, the lack of correlations between motor function and DTI metrics suggests other contributing factors to the HIV+women's motor deficits.

CNC EXPRESSION OF HIV-1 TAT PROTEIN PROMOTES HYPERGLUTAMATERGIC SIGNALING, INCREASED MORPHINE CONSUMPTION AND REINSTATEMENT OF EXTINGUISHED REWARD SEEKING

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Abstract Detail: Animal Study
Drug Category: Opiates/Opioids
Topic: HIV/Immune
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Expression of the HIV-1 transactivator of transcription (Tat) protein in the mouse CNS is sufficient to induce many deficits associated with HIV infection, and increases the rewarding effects of abused substances, but the underlying mechanisms are uncertain. As Tat has been reported to induce a hyperglutamatergic tone in medial prefrontal cortex (mPFC), we hypothesized that HIV-1 Tat expression in brain would increase voluntary consumption of morphine and promote reinstatement.
Methods: Using the iTat mouse model, where brain-selective Tat expression is controlled by activation of a doxycycline (Dox) promotor, we tested the effects of Tat protein on morphine-conditioned place preference (CPP) and voluntary morphine consumption in a two-bottle choice (TBC) assay. Dox-treated G-tg mice (lacking the Tat gene) served as controls. Glutamatergic signaling in mPFC was further assessed with electrophysiological measures in whole-brain slices isolated from Dox-treated iTat and G-tg mice.
Results: Dox-treatment of iTat, but not G-tg, mice significantly increased voluntary consumption of morphine over saline-treated littermates up to a week after Tat induction. Likewise, expression of Tat protein produced reinstatement of extinguished morphine place preference. Electrophysiological assessment found that exposure to Tat protein facilitated layer 2/3 pyramidal neuron firing in the mPFC of Dox-treated iTat mice. Consistent with these observations, treatment with the N2RB inhibitor ifenprodil or a glutaminase inhibitor attenuated the behavioral effects in iTat mice expressing Tat protein.
Conclusions: These data suggest that expression of HIV-1 Tat protein in mouse brain potentiated the voluntary consumption of morphine in an exposure-dependent manner and

induced reinstatement of extinguished morphine-seeking behavior, at least partially through the dysregulation of the glutamatergic system in mPFC. Moreover, these results suggest a biological means by which HIV infection may increase the vulnerability to substance abuse and relapse in abstinent subjects.

DNA METHYLATION MEDIATES THE EFFECT OF COCAINE USE ON HIV DISEASE SEVERITY AMONG HIV-POSITIVE PATIENTS

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Abstract Detail: Human
Drug Category: Stimulants
Topic: Genetics
Abstract Category: Original Research
Designation: M.S., Ph.D.

Abstract: Aim: Cocaine use accelerates HIV progression and worsens HIV outcomes. However, the mechanism is largely unknown. We aim to test whether DNA methylation in blood mediates the association between cocaine use and HIV disease severity in a veteran population (N=1,463).
Methods: HIV disease severity was measured by a well-established score, the Veteran Aging Cohort Study index (VACS index). We performed analyses to assess the association of cocaine use with VACS index and mortality in HIV-positive patients. Epigenome-wide DNA methylation of 408,583 CpG sites in blood was profiled. Epigenome-wide association analysis (EWA) on persistent cocaine use and VACS index was separately conducted. CpG sites that have $p<0.001$ in both EWA were selected for the mediation analysis, and we tested each CpG's mediation effect on the association between persistent cocaine use and VACS index.
Results: Cocaine use increased the risk of 10-year mortality in HIV-positive subjects (hazard ratio=1.09, 95%CI 1.01-1.18, p=0.039), and high cocaine use frequency was significantly associated with VACS index (p=3.8×10-3) adjusted for confounding factors. EWA selected 17 CpG sites for mediation analysis ($p < 0.001$ in both EWA) and 14 out of 17 CpG sites showed significant mediation effect on the association between persistent cocaine use and HIV severity (FDR < 0.05). Each of significant CpG explained from 12% to 38% variation of cocaine affecting HIV severity. These 14 CpG sites located in 12 genes that involved in inflammation process, HIV pathogenesis and progression (IFIT3, IFITM1, NLRC5, TAP1, TAP2, CX3CR1, PARP9, MX1, EPSTI1, FKBP5, PLSCR1, C13orf30). Furthermore, these genes were enriched on biological pathways of viral process (FDR= 0.0013), regulation of viral process (FDR= 0.0054), response to cytokine (FDR= 0.0174) and viral life cycle (FDR= 0.0476).
Conclusions: Several DNA methylation sites appear to mediate the effect of cocaine use on HIV disease severity.

INITIATION OF ANTIRETROVIRAL THERAPY WHILE IN THE HOSPITAL FOR PERSONS LIVING WITH HIV AND SUBSTANCE USE PREDICTS HIV TREATMENT LINKAGE AND RETENTION

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Abstract Detail: Human
Drug Category: Other, HIV & Substance use intersection
Topic: Treatment
Abstract Category: Original Research
Designation: M.D.

Abstract: Aim: Studies have demonstrated the positive benefits of ART initiation on the day of HIV testing or at the first clinical visit, regardless of CD4 count. The hospital setting has been understudied for immediate introduction of ART.
Methods: The National Drug Abuse Treatment Clinical Trials Network's Project HOPE recruited 801 HIV+ adult substance users in 11 hospitals across the US. This secondary analysis examined factors related to initiating ART in the hospital and its association with linkage to care, retention in HIV care and viral suppression. In addition, socio-demographic and other factors associated with initiating ART while hospitalized were explored.
Results: Of 801 study participants, 124 (15%) were initiated on ART in the hospital. The time to the first HIV primary care visit among those who initiated ART in the hospital was 29 days and 54 days among those who did not initiate ART in the hospital (p=0.0145). Initiating ART in the hospital was associated with increased HIV treatment retention (total number of hospital clinic/outpatient and doctor's office visits after the initial hospital discharge) at 6 months (aOR=1.39, 95% CI [1.02, 1.88]) and 12 months (aOR=1.53, 95% CI [1.15, 2.04]). There was no association between starting ART in the hospital and viral suppression at 6 or 12 months (OR=1.45, 95% CI [0.88, 2.40] and OR=0.8, 95% CI [0.53, 1.2], respectively). Participants from hospital sites in the South were less likely to initiate ART in the hospital compared to non-Southern sites (OR=0.40, 95% CI [0.27, 0.61]). Lifetime history of participation in alcohol or substance use treatment (OR=1.87, 95% CI [1.17, 2.98]) were associated with a greater likelihood of ART initiation in the hospital.
Conclusions: While these findings demonstrate potential benefits of initiating ART in the hospital in HIV infected patients with substance use, further research is needed to test the effectiveness of this approach.

Hormone

THE ROLE OF PROGESTERONE AND ESTRADIOL ON OPIOID SELF-ADMINISTRATION IN FEMALE RATS

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Abstract Detail: Animal Study
Drug Category: Opiates/Opioids
Topic: Behavior
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: We previously reported that heroin intake decreases during the proestrus phase of the estrous cycle in female rats. The purpose of this study was to (1) replicate these findings in Long-Evans (LE), Lewis (LEW) and Sprague-Dawley (SD) rats, (2) determine the hormonal mechanisms mediating proestrus-induced decreases in heroin intake by testing the effects of exogenous estradiol and progesterone on heroin intake in ovariectomized female rats, and (3) determine whether chronic administration of exogenous hormones decreases opioid intake in intact female rats.
Methods: In Experiment 1, the estrous cycle of intact, female LE, LEW, and SD rats was tracked daily and heroin intake was examined. In Experiment 2, separate groups of ovariectomized female LE rats were treated chronically with estradiol, progesterone, estradiol + progesterone, or vehicle, and heroin intake was examined. In Experiment 3, separate groups of intact female LE rats were treated chronically with either a low dose of estradiol, a high dose of estradiol, or vehicle, and heroin and remifentanil intake was examined.
Results: Heroin intake decreased significantly during proestrus in all three rat strains under at least one dose condition, and these effects were most robust in LE rats. In Experiment 2, estrogen-treated rats self-administered less heroin than any other group and significantly less heroin than rats treated with progesterone. In Experiment 3, chronic administration of estradiol non-significantly decreased heroin intake and significantly decreased remifentanil intake in intact female rats.
Conclusions: These data indicate that heroin intake decreases significantly during proestrus across rat strains and that these effects are likely mediated by estradiol. These data also indicate that chronic estradiol administration decreases opioid intake in intact female rats, suggesting that an estrogen-based pharmacotherapy may represent a novel treatment approach for women with opioid use disorder.

ESCALATION AND REINSTATEMENT OF FENTANYL SELF-ADMINISTRATION IN MALE AND FEMALE RATS

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Abstract Detail: Animal Study
Drug Category: Opiates/Opioids
Topic: Behavior
Abstract Category: Original Research
Designation: B.S.

Abstract: Aim: This study determined if escalation of fentanyl self-administration produces sex-dependent differences in craving, as measured by reinstatement of drug seeking following extinction.
Methods: Adult male (n=16) and female (n=19) Sprague-Dawley rats were trained to self-administer (SA) i.v. fentanyl (2.5 ug/kg/infusion) across seven daily 1-hr sessions, followed by

21 SA sessions of either 1- or 6-hr duration. Both groups then underwent 14 consecutive 1-hr extinction sessions. Reinstatement was assessed following pretreatment with either fentanyl (10 or 30 ug/kg, s.c.), the α2-adrenerigic antagonist yohimbine (1 or 2 mg/kg, i.p.) or vehicle.
Results: During the initial 1-hr acquisition sessions, females displayed greater active lever responding compared to males ($F_{6,196} = 2.15$, $p<0.05$). After rats were split into 1- and 6-hr SA groups, the 6-hr group escalated intake more than the 1-hr group ($t_{28.99} = 48.16$, $p<0.001$), regardless of sex. Across extinction sessions, both the 1- and 6-hr SA groups decreased active lever responding ($F_{13,364}=6.95$, $p<0.001$), although females responded more than males ($F_{13,364}=6.79$, $p<0.001$). Rats reinstated to either yohimbine ($F_{2,55} = 7.24$, $p=0.005$) or fentanyl ($F_{2,56} = 27.2$, $p=0.001$), but there were sex x group interactions for both drugs (yohimbine: $F_{1,28} = 5.16$, $p<0.05$; fentanyl: $F_{2,56} = 27.18$, $p=0.001$). For the 1-hr group, females responded more than males following either drug (yohimbine: $t_{28} = 3.67$, $p=0.001$, fentanyl: $t_{28} = 3.31$, $p<0.005$), while there was no sex difference in the 6-hr group. A priori testing within each sex revealed that the 6-hr group had greater fentanyl-induced reinstatement than the 1-hr group for males ($F_{2,28}=6.10$, $p<0.05$), but not for females.
Conclusions: Although initial acquisition of 1-hr fentanyl SA was more rapid in females, sex differences were not observed in escalation. However, for reinstatement, comparison between 1- and 6-hr groups showed that dysregulation of intake following escalation induced greater fentanyl seeking in males only.

SEX DIFFERENCES IN BRAIN GLUTAMATE AND CIGARETTE CRAVING

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Abstract Detail: Human
Drug Category: Nicotine/Tobacco
Topic: Sex Differences
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Women have more difficulty maintaining long-term abstinence from smoking than men, are disproportionately affected by certain serious smoking-related illnesses, and experience sex-specific effects of smoking. Prior research shows that compared to men, women report greater craving and withdrawal-related distress during abstinence from smoking, and greater relief when they resume smoking. Yet the neural mechanisms driving sex differences in these behavioral states remain unknown. Understanding these differences can inform the development of personalized smoking-cessation therapies. Previous studies suggest that brain glutamate concentration may differ between men and women and may play a key role in smoking-related behaviors.
Methods: We therefore tested for (1) sex differences (11 men and 9 women) in the effects of acute smoking on glutamate levels (Glu) in the dorsal anterior cingulate cortex (dACC), which has been highly implicated in Tobacco Use Disorder, using magnetic resonance spectroscopy; (2) sex differences in the relationship between dACC Glu and cigarette craving; and (3) the relationship between dACC Glu and ovarian hormone (estradiol and progesterone) levels.

Results: Pilot data show a significant interaction [F(1,18)=5.739, p=0.028] between sex (male vs female) and smoking state (abstinent vs post-smoking) on dACC Glu, with female smokers exhibiting lower dACC Glu than males (p=0.014) during abstinence, but not after smoking (p>0.05). In abstinent female smokers, but not males, lower dACC Glu was associated with greater cigarette craving (R2=0.370, p=0.014). There was also a strong negative trend between plasma estradiol (R2=0.258, p=0.067), but not progesterone (p>0.05), such that abstinent female smokers with low plasma estradiol exhibited greater dACC Glu.
Conclusions: These preliminary results provide evidence for sex differences in the neural substrates that underlie negative smoking-related states, which are a barrier to long-term abstinence and cessation. In addition, they suggest that increasing dACC Glu may be a promising therapeutic approach for smoking cessation in women, but not men.

SEX DIFFERENCES IN THE NEURAL AND ENDOCRINE RESPONSES TO STRESS AND ITS RELATIONSHIP TO OPIOID MISUSE

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Neurobiology
Abstract Category: Original Research
Designation: D.Phil.

Abstract: Aim: Stress increases pain sensitivity and risk of opioid misuse, and sex difference significantly contributes to this relationship. Women have more difficulties with stress, chronic pain, pain-related emotional disturbance, and greater potential risk of physical dependency compared with men, but the neural and endocrine processes underlying this relationship is unclear.
Methods: The current study examined sex-specific neurobiological responses underlying stress, chronic pain and risk for opioid misuse using multimodal neuroimaging that combines functional magnetic resonance imaging and hypothalamus-pituitary-adrenal (HPA) axis measures. Brain response to stress was examined in 53 individuals (age=36 (sd=10.1)) with chronic pain categorized by sex and opioid use status. Demographically-matched four groups included 22 control women, 21 control men, 5 women with regular opioid use (OU), and 5 OU men.
Results: A significant effect of Group X Sex X Condition was found in the ventromedial prefrontal cortex (VmPFC) (p<0.01, whole-brain corrected). Sex difference was only present in the OU group; the VmPFC response to stress was hypoactive in OU women, but hyperactive in OU men, and this pattern was significantly different from the control group. Cortisol response also showed a significant Sex X Group effect (F=4.9, p<0.05). Sex difference was significant only in the OU group (p<0.01), such that cortisol levels in OU women were lower than OU men, suggesting their disrupted HPA axis responses. Additionally, during the subsequent 60-days follow-up, increased opioid intake was associated with decreased VmPFC response to stress (p<0.01) and low cortisol levels (p<0.05).
Conclusions: These findings provide preliminary evidence of sex differences in neural and endocrine stress responses in opioid using men and women and its link to increased prescription

opioid use. Stress and chronic pain may result in sex-specific neuroadaptations in the VmPFC-HPA axis system, which may increase intake and risk of opioid misuse, especially in women.

GENDER-SPECIFIC EXAMINATION OF AGE TRAJECTORIES OF DRUG USE IN PERSONS DUALLY DIAGNOSED WITH COMBINED OPIOID AND COCAINE DEPENDENCE

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Abstract Detail: Human
Drug Category: Polydrug (i.e. Use of more than one drug combination)
Topic: Sex Differences
Abstract Category: Original Research
Designation: NP

Abstract: Aim: The aim of this study is to examine age trajectories of heroin and cocaine use in volunteers dually diagnosed with both opioid and cocaine dependence by DSM-IV criteria (OD+CD). We therefore examined age of first use, age of onset of heaviest use, and time of escalation (defined as age of onset of heaviest use minus age of first use) of both substances. Additionally, we examined if these trajectories differ by gender.
Methods: The protocol was approved by the Institutional Review Board of the Rockefeller University Hospital, and adult volunteers of both genders and varied ethnic/cultural backgrounds from the New York Metropolitan area signed an informed consent. Volunteers with OD+CD (n=215, female=76) were sequentially ascertained by a clinician, with the SCID-I interview for DSM-IV psychiatric diagnoses and KMSK scales for dimensional measures of drug exposure.
Results: In these volunteers with OD+CD, age of first use of heroin and cocaine were positively correlated, in both males (Spearman r=0.42, p<0.0001) and females (r=0.48, p<0.0001). Similarly, age of onset of heaviest use of heroin and cocaine were positively correlated in both males (r=0.39, p<0.0001) and females (r=0.37, p<0.0001). Age of first use of cocaine was significantly earlier than heroin in males (median age 18 years and 20 years respectively; Wilcoxon test p=0.0061), but not in females (median ages 19 years and 20.5 years respectively; Wilcoxon test p=NS). Time of escalation of heroin and cocaine use were also positively correlated with each other in both males (r=0.34, p<0.0001) and females (r=0.51, p<0.0001).
Conclusions: A greater proportion of male volunteers with OD+CD commenced cocaine use before heroin; this finding was not evident in females. Both male and female subjects with rapid escalation of heroin use also tend to have rapid escalation of cocaine use.

THE EFFECTS OF ESTRADIOL AND PROGESTERONE ON HEROIN- AND SUCROSE-MAINTAINED RESPONDING

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Abstract Detail: Animal Study

Drug Category: Opiates/Opioids
Topic: Behavior
Abstract Category: Original Research
Designation: D.Phil.

Abstract: Aim: We previously reported that heroin intake decreases during the proestrus phase of the estrous cycle in female rats. Estradiol and progesterone rise and fall in rapid succession during proestrus, and therefore it is not known which of these two hormones contribute to the decrease in heroin intake observed during proestrus. The purpose of this study was to examine the effects of estradiol and progesterone on heroin self-administration and to determine if proestrus-induced decreases in responding extended to a nondrug reinforcer.
Methods: In Experiment 1, the estrous cycle of intact female rats was tracked daily and either the estrogen-receptor antagonist, raloxifene, the progesterone-receptor antagonist, mifepristone, or their combination was administered 30 minutes prior to a heroin self-administration session. In Experiment 2, an artificial proestrus state was experimentally induced in ovariectomized rats by administering estradiol (or vehicle) 22 hours and progesterone (or vehicle) 30 minutes before a heroin self-administration session. In Experiment 3, the effects of the estrous cycle on responding maintained by sucrose was examined.
Results: In Experiment 1, raloxifene, but not mifepristone, significantly blocked proestrus-induced decreases in heroin intake in female rats. In Experiment 2, estradiol administered 22 hours before a test session significantly decreased heroin intake in ovariectomized rats, and this effect was independent of progesterone administration. In Experiment 3, responding maintained by sucrose did not decrease during proestrus in intact female rats.
Conclusions: These data indicate that responding maintained by heroin, but not a nondrug reinforcer, significantly decreases during proestrus in female rats, and that these effects are mediated by estradiol but not progesterone.

Nonfatal Overdose

BUPRENORPHINE TREATMENT UPTAKE FOLLOWING A NON-FATAL OVERDOSE: ASSOCIATIONS WITH OPIOID-RELATED MORTALITY

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Other
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Buprenorphine is a medication-assisted treatment (MAT) in an effective treatment for opioid-related harms, including overdose. Yet, few studies have investigated whether this MAT reduces the risk of opioid-related mortality following a non-fatal opioid-related overdose exposure. This paper had two primary objectives: 1) to profile sociodemographic characteristics of survivors and descendants, including prescription drug

touchpoints and critical encounters; and 2) to examine the main and interaction effects between sociodemographic characteristics, prescription drug and critical encounters in association with fatal drug poisoning.
Methods: A retrospective study was conducted on all overdose cases in Marion County, Indiana in 2017. Data were linked from multiple sources, including, Indiana Department of Public Health; Indiana State Police; Indiana Department of Correction; and prescription drug monitoring program (PDMP). Cases were linked to vital records to assess mortality. Exposure to MAT was measured by if a buprenorphine prescription was dispensed in the 12-months following the first non-fatal opioid-related overdose. Bivariate analyses were conducted to assess group differences between survivors and decedents. A series of multiple logistic regression models were used to determine main and interaction effects of opioid-related mortality.
Results: Among the 10,080 non-fatal overdoses, 2.4% (247) resulted in a subsequent fatal overdose. Decedents were on average younger (M = 36.4), White, male, and 83.8% (n = 207) did not have a current buprenorphine prescription. Individuals with an arrest were 2.51 (95% CI = 1.90-3.31, p = .001) times more likely to experience a fatal overdose. Those with a buprenorphine prescription were 66% (95% CI = 0.47-0.93) less likely to experience a fatal overdose. A buprenorphine prescription was a significant moderator of the relationship between an arrest encounter and opioid-related mortality.
Conclusions: Linking data sources had utility in identifying risk and protective factors of fatal overdose. Criminal justice involvement remains an area of attention for potential MAT overdose prevention interventions.

DEVELOPING AND TESTING A SMARTPHONE APP TO DELIVER NALOXONE TO OPIOID OVERDOSE VICTIMS IN PHILADELPHIA

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Prevention
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Philadelphia has the highest drug overdose rate among any large city in the U.S. Community-based overdose prevention programs, whereby lay responders administer naloxone to victims during overdose events, has been one response to the overdose crisis in Philadelphia and elsewhere. We sought to develop and field test a smartphone app called UnityPhilly to link lay responders carrying naloxone to individuals experiencing opioid overdose events in real time.
Methods: In 2019, 97 persons living/working in the Kensington neighborhood of Philadelphia - 52 community members and 45 active opioid users – were recruited as UnityPhilly responders and completed a survey on past/current drug use, downloaded UnityPhilly onto their cellphone, and received overdose prevention training/naloxone. Afterwards, responders' complete

monthly surveys and incident reports on use/non-use of UnityPhilly. Over 200 doses of 4 mg intranasal naloxone were distributed to study participants.
Results: UnityPhilly responders were predominantly non-Hispanic white (66.0%), female (50.7%), and averaged 38.2 years old. Most reported lifetime opioid misuse (71.7%) and/or medication-assisted treatment (48.5%). Between March and December 2019, 84 opioid overdose events were signaled using UnityPhilly, and one or more UnityPhilly responder arrived at the overdose location in 33 cases (39.3%). Among these 33 events, 52 doses of naloxone was administered to an overdose victim. Across all 33 events, a total of 52 UnityPhilly responders (2.1 responder per event) arrived at the overdose location.
Conclusions: UnityPhilly is the first field-tested app in the U.S. to connect lay responders carrying naloxone. Equipped with UnityPhilly, community members and active opioid users were able to signal an overdose, respond to the event, and deliver/administer naloxone to an overdose victim. UnityPhilly supplemented traditional emergency medical systems system with its network of responders equipped with app, naloxone, and real time response capabilities.

EFFECT OF RECURRENT OVERDOSE AND MEDICATION FOR OPIOID USE DISORDER ON MORTALITY: A SURVIVAL ANALYSIS

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Treatment
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: The study aims to explore the effect of recurrent overdose on mortality and evaluate the effectiveness of medication for opioid use disorder (MOUD) among the WV Medicaid population. The hypothesis is that recurrent overdose has negative effect and MOUD has positive effect on patients' survival rates.
Methods: The occurrence of first nonfatal overdose was identified as index overdose and starting date; an overdose cohort was then determined to allow 12 months of observation before and after the index overdose. The primary outcome events include recurrent overdose (nonfatal) and all-cause mortality. Kaplan–Meier method and log-rank test were used to assess the time-to-events between subgroups.
Results: A total of 446565 consecutively enrolled WV Medicaid beneficiaries from 2014 to 2016 were analyzed and 2081 had overdose reported; 261 (12.5%) experienced recurrent overdoses, and 127 (6.1%) died within 12 months. People who experienced a recurrent overdose in the 12-month following the index overdose had a significantly decreased survival rates, compared with those who did not (90% vs 94%; $p = 0.012$). Those who had received any MOUT ($N = 483$) and those who had longer duration (> 87 days) receiving MOUT were both significantly associated with lower mortality rates ($p = 0.039$ and 0.046, respectively). However, only 139 (15%) of the 2081 with overdoses first initiated their MOUT within 12 months after the index overdose, and preliminary analysis indicated that those initiating MOUT earlier (less than 122 days after the index overdose) had a non-significantly higher mortality rate than those starting later (over 122 days after the index overdose).

Conclusions: Recurrent nonfatal overdoses significantly increase mortality risk. We confirm findings that MOUT is effective in preventing death. However, findings that mortality may be increased in those receiving early initiation of MOUT post overdose is concerning and is being investigated further.

Opioid Medication Development

PHARMACODYNAMIC EFFECTS, PHARMACOKINETICS, AND METABOLISM OF THE NOVEL SYNTHETIC OPIOID, U-47700, IN MALE RATS

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Abstract Detail: Animal Study
Drug Category: Opiates/Opioids
Topic: Mechanisms of Action
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Fentanyl and its analogs are fueling an epidemic of opioid overdose deaths. Moreover, non-fentanyl opioid compounds are appearing in street drug markets as adulterants in heroin or counterfeit pain pills. 3,4-Dichloro-N-[(1R,2R)-2-(dimethylamino)cyclohexyl]-N-methylbenzamide (U-47700) is a non-fentanyl mu-opioid agonist linked to overdose deaths. Here, we examined the pharmacodynamic effects, pharmacokinetics, and metabolism of U-47700 in rats.
Methods: Male Sprague-Dawley rats received surgically-implanted intravenous (i.v.) catheters and subcutaneous (s.c.) temperature transponders under ketamine/xylazine anesthesia. After one week, rats received s.c. U-47700 HCl (0.3, 1.0 or 3.0 mg/kg) or its saline vehicle, and blood samples (0.3 mL) were collected via i.v. catheters at 15, 30, 60, 120, 240, 480 min post-injection. Plasma was assayed for U-47700 and its N-desmethyl metabolites by liquid chromatography tandem mass spectrometry. Pharmacodynamic effects, including hot plate latency, catalepsy, and core temperature, were assessed at each blood withdrawal.
Results: U-47700 induced dose-related increases in hot plate latency and catalepsy, while 3.0 mg/kg caused marked hypothermia. Plasma concentrations of U-47700 rose linearly with increasing dose, and Cmax was achieved rapidly, with Tmax of 15-38 min. Cmax values for the N-desmethyl and N,N-didesmethyl metabolites were delayed, with Tmax ranging from 90-384 min. After the 3.0 mg/kg dose of U-47700, mean Cmax values for U-47700, N-desmethyl, and N,N-didesmethyl metabolites were 173, 102, and 236 ng/mL, respectively. Analgesia and catalepsy were correlated with plasma U-47700, and these relationships displayed counter-clockwise hysteresis.
Conclusions: U-47700 induces dose-related analgesia and catalepsy, consistent with its mu-opioid receptor agonist activity. The drug displays linear kinetics, and its N-desmethyl metabolites achieve mean Cmax values in the same range as the parent compound, with sustained half-lives. Pharmacodynamic effects of U-47700 are closely related to plasma concentrations of the parent compound, but a role of the metabolites cannot be ruled out.

LORCASERIN TREATMENT FOR EXTENDED RELEASE NALTREXONE INDUCTION AND RETENTION FOR OPIOID USE DISORDER INDIVIDUALS: A PILOT, PROOF-OF-CONCEPT RANDOMIZED TRIAL

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Treatment
Abstract Category: Original Research
Designation: M.D.

Abstract: Aim: Opioid Use Disorder (OUD) is a substantial public health problem. While effective pharmacotherapies are available, limitations exist. One factor impacting the uptake of extended-release naltrexone (XR-NTX) is that induction onto XR-NTX is often more difficult than buprenorphine, even in inpatient settings, and it is recommended that patients abstain for 7 days prior to initiating XR-NTX. Preclinical data suggest lorcaserin, a serotonin receptor (5HT-2C) agonist, may reduce opioid withdrawal. The aim of this trial was to determine if lorcaserin improves XR-NTX induction rates and mitigates withdrawal symptoms as compared to placebo in an outpatient setting.
Methods: This randomized double-blind trial included 49 adults (both males and females) with OUD. After a brief detoxification (ranging from 2-7 days), participants were inducted onto XR-NTX. At the initiation of detoxification, individuals were randomized to lorcaserin or placebo, plus ancillary medication, and were maintained on lorcaserin or placebo for the subsequent 6-weeks. The primary outcome was the proportion of individuals who received the first XR-NTX injection. Secondary outcomes were withdrawal and those receiving the second XR-NTX injection.
Results: The proportion of participants receiving the first lorcaserin: 36%; placebo: 44%) and the second lorcaserin: 27%; placebo: 31%) XR-NTX injections were not significantly different between treatment arms (P=.62; P=.77, respectively). Prior to the first injection, withdrawal scores did not significantly differ between treatment arms over time (arm*visit interaction P = .12).
Conclusions: Lorcaserin failed to improve outpatient XR-NTX induction rates. Instead, both study arms had lower induction rates than a prior outpatient study using common ancillary medications alone to induct individuals onto XR-NTX. One possibility is that high rates of highly potent synthetic opioids use among those with OUD complicate detoxification and pharmacologic approaches used to induct individuals onto XR-NTX in outpatient settings. Future studies might explore new methods to induct OUD participants in outpatient settings.

THE CB1 POSITIVE ALLOSTERIC MODULATOR, ZCZ011, ATTENUATES NALOXONE-PRECIPITATED WITHDRAWAL SIGNS IN OXYCODONE-DEPENDENT MICE

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Abstract Detail: Animal Study
Drug Category: Marijuana/Cannabinoids
Topic: Behavior
Abstract Category: Original Research
Designation: B.Sc.

Abstract: Aim: Evaluate whether the CB1 positive allosteric modulator, ZCZ011, attenuates naloxone-precipitated somatic withdrawal signs in oxycodone-dependent mice.
Methods: Male and female CD-1 mice were administered daily subcutaneous (s.c.) injections of oxycodone (in 0.9% saline) for eight days with increasing doses of 9, 17.8, 23.7, and 33 mg/kg oxycodone b.i.d. (~7 h separating injections) on days 1-2, 3-4, 5-6, 7-8, respectively. On the morning of day 9, mice were administered 33 mg/kg oxycodone, 2 h later administered s.c. naloxone (1 mg/kg), and immediately recorded for 30 min. An observer blinded with respect to condition scored somatic withdrawal signs including jumping, paw flutters, head shakes, diarrhea, and decrease of body weight. We evaluated whether an intraperitoneal injection of the CB1 PAM, ZCZ011 (5, 10, 20, or 40 mg/kg; n=16 male and female mice/treatment), administered 75 min prior to naloxone would attenuate somatic withdrawal signs relative to vehicle-treated mice (mix of ethanol, emulphor-620, and 0.9% saline in a 1:1:18 ratio). Data were analyzed using one-way between measures analysis of variance. Tukey's post-hoc test was used for comparison between various treatments. The percentage of mice between groups presenting with diarrhea was compared with Fisher's exact test.
Results: ZCZ011 attenuated paw flutters ($F(4,74) = 8.7$; $p < 0.0001$), head shakes ($F(4,74) = 3.8$; $p = 0.007$), body weight loss ($F(4,75) = 6.8$; $p < 0.0001$), and the occurrence of diarrhea (Fisher's: $p < 0.001$). However, ZCZ011 did not attenuate jumping behavior ($F(4,74) = 0.47$; $p = 0.79$).
Conclusions: These findings suggest that CB1 PAMs offer a promising strategy to treat opioid withdrawal.

VENTILATORY-DEPRESSANT EFFECTS OF LORCASERIN IN RHESUS MONKEYS

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Abstract Detail: Animal Study
Drug Category: Opiates/Opioids
Topic: Drug Interactions
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Lorcaserin, a drug with agonist properties at serotonin 2C receptors, is currently approved in the US for treating obesity (Belviq®) and is being investigated as a treatment for substance use disorders (SUD) including opioids. If lorcaserin is used for treating SUD, it will likely be co-administered with other drugs. Thus, it is important to explore adverse effects that might emerge when lorcaserin is combined with these other drugs. The goal of this project was to examine interactions between lorcaserin and opioids with regard to ventilatory

depression, which is the primary cause of death from an opioid overdose. This study determined effects of the mu opioid receptor agonist morphine and lorcaserin alone on ventilation in order to set the stage for subsequent tests with drug combinations.
Methods: Four rhesus monkeys (3 females and 1 male) served as subjects, and minute volume was measured using head plethysmography. On separate occasions, dose-effect curves for morphine (1.0-10 mg/kg) or lorcaserin (0.1-3.2 mg/kg), administered subcutaneously, were determined using a cumulative dosing procedure with 15-min inter-injection intervals.
Results: Under control conditions, mean (± 1 SD) minute volume was 2017 (± 206) ml/min. Morphine and lorcaserin both dose-dependently decreased minute volume with doses of ≥ 5.6 mg/kg of morphine and ≥ 1.0 mg/kg of lorcaserin decreasing minute volume by > 25% of control; the largest dose of lorcaserin studied (3.2 mg/kg) decreased minute volume by > 40%.
Conclusions: The ventilatory-depressant effects of opioids are well-documented, and effects of morphine in the current study are consistent with the literature. Lorcaserin also decreased minute volume at doses that have been shown to attenuate the abuse-related (e.g., reinstatement) effects of opioids in rhesus monkeys. These data suggest that combining lorcaserin and opioids could increase the risk of ventilatory depression and, thus, overdose.

STUDIES OF CONTINUOUS LORCASERIN PLUS BUPRENORPHINE IN RAT FENTANYL SELF-ADMINISTRATION

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Abstract Detail: Animal Study
Drug Category: Opiates/Opioids
Topic: Substance Use Disorder
Abstract Category: Original Research
Designation: B.S.

Abstract: Aim: Opioid overdose deaths and prevalence of opioid use disorder (OUD) have reached crisis levels in the United States. Treatment with therapeutics such as the partial μ-opioid receptor agonist buprenorphine mitigate withdrawal, reduce mortality, and reduce intake of abused opioids (e.g., fentanyl, heroin). Still, the opioid epidemic has crystalized the need to identify adjunctive therapeutics to substantially improve the odds of successful recovery. In the present study, we tested the hypothesis that treatment with the FDA-approved 5-HT2CR agonist lorcaserin (Belviq®), previously shown to reduce opioid intake in the preclinical self-administration model, may serve as an efficacious adjunct to suppress opioid intake and/or prevent escalation of opioid use after cessation of buprenorphine treatment. We employed osmotic minipumps to chronically administer buprenorphine and/or lorcaserin to achieve stable levels and mimic a clinical dosing regimen.
Methods: Male Sprague-Dawley rats (n=34) were implanted with osmotic minipumps [sham, lorcaserin (1 mg/kg/day), buprenorphine (3 mg/kg/day), or the combination] following stable acquisition of fentanyl self-administration. Rats resumed fentanyl self-administration for 10 days and were then monitored for an additional ten days after removal of osmotic pumps. During this phase, the efficacy of acute lorcaserin (1 mg/kg, s.c.) to impact fentanyl intake was assessed.

Results: Chronic treatment with buprenorphine or the combination, but not lorcaserin alone, attenuated fentanyl intake relative to sham-operated rats [$F_{3,30}=15.3$, $p<0.05$]. However, chronic treatment with buprenorphine was not significantly different than combination treatment with buprenorphine plus lorcaserin. Acute treatment with lorcaserin attenuated fentanyl intake relative to saline-treated rats [$F_{1,12}=51.81$, $p<0.05$].
Conclusions: The efficacy of acute lorcaserin to suppress opioid intake extended to the illicit opioid fentanyl. Further, chronic buprenorphine, with or without lorcaserin, resulted in sustained inhibition of fentanyl intake. Taken together, these studies provide support for further interrogation of the efficacy or lorcaserin as a viable adjunct pharmacotherapy to combat OUD.

Opioid Treatment

A RANDOMIZED TRIAL OF PSYCHOSOCIAL TREATMENT INTENSITY FOR PATIENTS WITH OPIOID USE DISORDER INDUCTED ON BUPRENORPHINE/NALOXONE

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Treatment
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: The literature has provided limited evidence that receiving psychosocial services improves outcomes for patients using buprenorphine/naloxone (BUP/NX) for opioid use disorder (OUD), with questions remaining about appropriate levels of treatment intensity. This randomized trial compared two group-based models of care among patients with OUD inducted on BUP/NX in specialty substance use treatment.
Methods: 213 patients with OUD inducted onto BUP/NX were enrolled in the study, based in a substance use treatment clinic in an integrated health care system. Patients were randomized to a less intensive (1x/week), more medically focused treatment (MFT, n=111) or usual care (4x/week intensive outpatient treatment, n=102). Baseline, 6- and 12- month follow-up interviews were conducted to assess medication adherence and abstinence. Medication adherence was also measured with pharmacy data from the electronic health record (EHR). General estimating equation (GEE) models examined outcomes, controlling for age, gender, drug use severity and treatment length of stay.
Results: There were no differences in treatment retention between the two arms. Compared to usual care (UC), those in the MFT arm had higher buprenorphine adherence based on EHR data, measured as proportion of days covered >=90% (OR=2.62, 95% CI 1.15-5.95, $p<0.05$) and self-report of continuous use (OR=2.31, 95% CI 1.04-5.15, $p<0.05$) at 6 months. There were no significant differences in substance use at either 6 or 12 months (both arms had opioid abstinence rates >90%). However, model findings suggested greater improvement in mental health quality of life over 12 months for the MFT arm (LSMeans 6.72, 95% CI 5.13-8.32 vs 4.34, 95% CI 2.68-6.00, $p<0.05$).

Conclusions: Findings suggest that receiving less intensive psychosocial services was not less effective for treatment retention and may be related to improved medication adherence. Flexible options should be offered to patients who may be unable to attend highly structured programs. Future research should examine sub-populations.

A RANDOMIZED TRIAL OF BRIEF COUNSELING FOR VETERANS WITH PTSD SERVICE-CONNECTION CLAIMS AND RISKY SUBSTANCE USE

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Abstract Detail: Human
Drug Category: Alcohol
Topic: Treatment
Abstract Category: Original Research
Designation: M.D.

Abstract: Aim: The service-connection application is an important point-of-contact for referring Veterans to treatment for their presenting complaint. Among PTSD claimants who also reported risky substance use, we tested a counseling intervention targeting treatment engagement and risky substance use.
Methods: Veterans presenting for service-connection examinations for PTSD in Connecticut and Tennessee were recruited. Those reporting risky substance use were randomly assigned to Brief Counseling or Treatment-as-Usual. Participants assigned to Brief Counseling were offered a single meeting with a study therapist with a follow-up telephone call. Participants completed assessments of risky substance use (timeline follow-back calendars) and PTSD (CAPS version 4) at baseline and 4 and 12 weeks after randomization. Fingernails were collected at baseline and week 12 for ETG analysis and use of VA services was extracted from the electronic medical record.
Results: Among 349 Veterans evaluated, 172 reported risky substance use and were randomized. Their mean age was 32.6 years and 87% were male. Counseling was attended by 49 of the 85 Veterans offered it. Study attrition was higher in the Tennessee site, and dropout was significantly associated with baseline lower last-month income and higher PTSD severity only in the Connecticut sample. Study counseling was associated with a significantly higher median number of VA mental health/substance use treatment sessions attended ($p<.01$), but groups did not differ in weeks of risky substance use, nail evidence of alcohol use or PTSD severity over time.
Conclusions: Substantial proportions of Veterans applying for PTSD-related service-connection reported risky substance use and chose to attend counseling offered to them. Brief counseling showed promise for engaging Veterans in VA behavioral treatments but did not impact risky substance use or PTSD during the 12-week follow-up. This is the third clinical trial of Veterans seeking service-connection in which counseling was associated with increased use of targeted VA service.

SUBSTANCE USE TREATMENT ENTRY IN A RANDOMIZED CLINICAL TRIAL OF PATIENT NAVIGATION SERVICES TO AVOID REHOSPITALIZATION (NAVSTAR)

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Treatment
Abstract Category: Original Research
Designation: B.A.

Abstract: Aim: To examine outcomes related to substance use treatment linkage among participants who received a patient navigation intervention compared to usual care.
Methods: Participants (N = 400) were hospitalized medical and/or surgical patients with a current diagnosis of opioid, cocaine, or alcohol use disorder enrolled in the Navigation Services to Avoid Rehospitalization (NavSTAR) study. Participants were randomized to either treatment-as-usual (TAU) or the NavSTAR intervention, which included care coordination and support for substance use and medical needs from a Masters-level patient navigator for 3-months post-discharge. Follow-ups were conducted at 3-, 6-, and 12-months post-discharge. Group differences in treatment entry were compared using chi-square tests of independence. Time-to-first episode of substance use treatment was examined using Cox proportional hazards regression.
Results: Self-reported treatment entry information was ascertained for 80%, 75%, and 68% of the sample at 3-, 6-, and 12-months, respectively. There were significant group differences in treatment entry within 3- (50.3% NavSTAR v. 35.3% TAU, p = 0.007) and 6-month (63.5% NavSTAR v. 46.8% TAU, p = 0.004), but not within 12-month follow-up (72.6% NavSTAR v. 65.1% TAU, p = 0.18). Time-to-event analysis found that NavSTAR participants had a higher likelihood of entering treatment within the 12-month follow-up period compared to TAU participants (HR = 1.43, 95% CI = 1.07, 1.91; p = 0.01). Likewise, among participants with opioid use disorder (OUD), participants in the NavSTAR condition were more likely to enter medication treatment for OUD within the post-discharge follow-up period compared to participants in the TAU condition (HR = 1.51, 95% CI = 1.09, 2.10, p = 0.01).
Conclusions: Patient navigation may be an effective post-discharge strategy to link hospitalized patients with comorbid substance use disorders to treatment services once they have been discharged to the community.

BUPRENORPHINE EXTENDED-RELEASE IN JAIL AND AT RE-ENTRY: PILOT PROOF-OF-CONCEPT VS. DAILY SUBLINGUAL BUPRENORPHINE-NALOXONE

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Treatment
Abstract Category: Original Research
Designation: M.D., M.Sc.

Abstract: Aim: Extended-release buprenorphine (XR-B) is newly FDA approved and its effectiveness in a criminal justice setting is promising but untested. This is an ongoing 8-week pilot proof-of-concept randomized controlled trial, open-label and unblinded, examining the feasibility and acceptability of buprenorphine extended-release (XR-B) vs. daily sublingual buprenorphine-naloxone (SL-B) for the treatment of opioid use disorder (OUD) in jail and at community re-entry, N=50.
Methods: This pilot is recruiting from within the standard-of-care NYC jail opioid treatment program, at NYC Jails. Potential participants currently maintained on sublingual buprenorphine (currently a NYC jail standard of care) are offered study information and encouraged to enroll. Participants are randomized 1:1 to either XR-B or SL-B approximately a week before their release date. Post-release there are five follow-up community visits all conducted at Bellevue Hospital Center in NYC. Participants assigned to XR-B receive at least one additional XR-B injection in the community.
Results: We have randomized 38 (21 SL-B; 17 XR-B) of target sample size, N=50. Mean age 43 (SD 9.9); 87% male; 45% Hispanic; 52% employed prior to incarceration. At baseline, 79% reported opiate/heroin use in the 30 days prior to incarceration; 37% of which was IV injection. Mean lifetime treatment intake episodes of any medication for OUD is four (SD 2.9); 89% tried buprenorphine treatment prior to in-jail program participation. Of the 38 randomized subjects, all have re-entered the community; 76.3% confirmed licit buprenorphine use; 76.4% (XR-B) retained in treatment, 76.2% (SL-B) retained in treatment.
Conclusions: XR-B has several potential advantages vs. SL-B notably the near zero probability of diversion and an improved, long acting "bridge" of medication adherence at release. Early rates of treatment retention show promising results for XR-B. Open-ended interviews conducted at the final study visits with patients will shed light on treatment satisfaction and in-jail experiences with XR-B.

A PROSPECTIVE LONGITUDINAL STUDY OF DIFFERENT OVERDOSE EDUCATION AND NALOXONE DISTRIBUTION MODELS AMONG INDIVIDUALS WITH OPIOID USE DISORDER

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Behavior
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Overdose education and naloxone distribution (OEND) is a harm reduction strategy shown to save lives. OEND trains laypersons in opioid overdose risk factors, how to recognize an opioid overdose, and how to intervene using the opioid antagonist, naloxone. The current trial evaluated the benefits of a novel in-depth, skills-based overdose education curriculum, compared to basic training (brief information only).
Methods: Individuals with opioid use disorder (OUD) all received basic OEND training and were required to engage a significant other (SO: e.g., a spouse, relative, or friend). Participants were randomized to one of three training conditions. One-third of the participants, along with their SO, were randomized to receive no additional training regarding opioid overdose (Treatment as Usual: TAU). One-third of the participants received extended training (ET) while their SO received only basic training. The final third received ET along with their SO (ETwSO). Participants were followed over the course of 1 year to assess retention of knowledge and naloxone utilization at 1, 3, 6 and 12 months after training.
Results: Three hundred and fourteen participants were randomized. The study found all forms of overdose education significantly increased skills, knowledge, and competency (vs pre-training baseline p's < 0.01). Participants reported 167 OD reversals with a 97% success rate. Extended training significantly increased the likelihood that participants would utilize naloxone by ~20% (vs TAU: $p < 0.05$). Furthermore, the most robust and sustained effect on naloxone utilization was found among participants who received extended training with a significant other (ETwSO vs ET and TAU: $p < 0.05$).
Conclusions: These results add to the growing body of literature demonstrating the efficacy of OEND as an opioid overdose harm reduction tool. Findings from this trial also reveal that there are ways to improve the effectiveness of existing programs, supporting the need for further empirical evaluation.

RESULTS OF THE DEBUT STUDY – A MULTISITE, OPEN-LABEL RCT OF WEEKLY AND MONTHLY DEPOT BUPRENORPHINE INJECTIONS (CAM2038) VS. DAILY SUBLINGUAL THERAPY INVESTIGATING PATIENT REPORTED OUTCOMES IN TREATMENT OF OPIOID USE DISORDER

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Treatment
Abstract Category: Original Research
Designation: M.D., Ph.D., Prof. Dr.

Abstract: Aim: To report results of the 24-week, randomized, open-label, active-controlled, multisite clinical trial, DEBUT, of weekly and monthly buprenorphine injections (CAM2038) versus standard of care (SOC) with daily sublingual buprenorphine (SL BPN; e.g. Suboxone® Film) in 120 outpatients at six clinical sites in Australia.
Methods: The primary efficacy analysis was the Treatment Satisfaction Questionnaire for Medication (TSQM) global satisfaction score. Secondary outcomes were TSQM effectiveness,

convenience and safety domain scores and other validated patient reported outcome measures of quality of life, burden of treatment and health economics. Questionnaires were administered by independent researchers at Baseline (Day 1), Weeks 4, 12, and 24/premature discontinuation. Retention, cravings., withdrawal, and illicit opioid use as well as safety and tolerability were also investigated.
Results: Of the 120 randomized participants, 60 received treatment with CAM2038 and 59 with SL BPN. Superiority was demonstrated for the primary endpoint of the TSQM global satisfaction with a score of 82.46 (77.9, 87.05) for CAM2038 versus 74.31 (69.73, 78.88) for SL BPN (p=0.0143). Significant improvements versus SOC were also seen in TSQM effectiveness and convenience domain scores, p<0001. Significant treatment differences were also seen for patient reported measures of quality of life, burden of treatment, and patient functioning. Retention in treatment with CAM2038 was high; with an 88% retention rate at week 24. Safety and tolerability were consistent with the well-known safety profiles of buprenorphine and CAM2038.
Conclusions: The DEBUT study, performed in real-world treatment setting with validated patient reported outcomes, met the primary endpoint, demonstrating superiority for global patient satisfaction, as well as improved outcomes for several secondary outcomes.

YOUNG ADULTS HAVE WORSE OUTCOMES THAN OLDER ADULTS: SECONDARY ANALYSIS OF THE XBOT TRIAL OF EXTENDED RELEASE NALTREXONE VERSUS BUPRENORPHINE FOR OPIOID USE DISORDER

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Other
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Young adults are disproportionately affected by the current opioid crisis. Medications for opioid use disorder (MOUD) have robust evidence of effectiveness among adults in general; however, the comparative effectiveness of different MOUD among young adults compared to older adults is less well understood.
Methods: This secondary analysis compared a young adult cohort (ages 18-25) to older adults (26+) who were included in a large comparative effectiveness trial ("XBOT") of extended release naltrexone (XR-NTX) vs. buprenorphine-naloxone (BUP-NX; Lee, 2018). Subjects were randomized to treatment with either XR-NTX or BUP-NX for six months. As in the parent study, the main outcome of opioid relapse was tested both within the intent to treat (ITT) sample (N = 570; all randomized participants) as well as among the per-protocol sample (n = 474; only those who inducted onto the randomly assigned medication).
Results: Among subjects in the ITT sample, a main effect of age group was found, with higher rates of relapse among young adults (70.3%) compared to older adults (58.2%), with an odds ratio (OR) of 1.72, (95% CI=[1.08, 2.70]) p=0.02. Likewise, in the per protocol sample, a main effect of age emerged such that overall rates of relapse were higher among young adults

(66.3%) compared to older adults (50.8%), HR 1.91 (95% CI=[1.19, 3.06]). Among the ITT sample, a survival curve analysis revealed a significant time-by-age group interaction (p = .01), such that relapse risk did not differ by age group at the start of the study period, but by week 8 the risk of relapse was significantly and progressively higher in the young adult group through week 24.
Conclusions: Young adults have additional vulnerabilities that increase their risk for opioid relapse, regardless of medication. These results suggest that specialized, developmentally informed interventions may be needed for successful treatment of OUD among young adults.

TREATMENT OUTCOMES IN INDIVIDUALS WHO FAILED AN INITIAL OUTPATIENT NALTREXONE INDUCTION ATTEMPT

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Substance Use Disorder
Abstract Category: Original Research
Designation: M.D.

Abstract: Aim: An outpatient protocol for detoxification and long acting naltrexone (XR-NTX) induction is successful for many patients. However, about 40-60% of patients are unable to initiate XR-NTX due to continued opioid use or intolerable withdrawal symptoms. This open label non-randomized study evaluated a new approach to initiate XR-NTX in patients who failed the first attempt at induction but are interested in detoxification and XR-NTX treatment.
Methods: Individuals participating in clinical trials of an outpatient XR-NTX induction (one week or two-week protocols) who were unable to initiate XR-NTX were recruited to participate in this follow up trial. They were stabilized on buprenorphine (8 mg per day) for one week, slowly tapered to 2 mg/day over the subsequent three weeks, and after two-day buprenorphine washout received a four-day ascending titration of oral naltrexone.
Results: Thirty patients who failed their initial induction attempt were recruited for participation. Of these, 8 (27%) were successfully inducted onto XR-NTX following an extended buprenorphine taper. An additional seven participants continued on buprenorphine maintenance treatment; six participants had continued opioid use during the taper period, and one did not tolerate oral naltrexone. The remaining 15 participants dropped out of treatment and were lost to follow up.
Conclusions: About one quarter of individuals who failed an initial outpatient XR-NTX induction procedure was successfully inducted using a modified procedure involving a slow buprenorphine taper. An additional quarter of participants was also able to successfully transition to buprenorphine maintenance. A repeated induction approach involving a slow buprenorphine taper may therefore be a reasonable approach to re-attempt induction in individuals who fail a more rapid approach. Further studies with a larger sample and with random assignment can more definitely determine the optimal course of action for these patients.

ACTIVITY IN THE ORBITOFRONTAL CORTEX IS REQUIRED FOR OXYCODONE CRAVING

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Abstract Detail: Animal Study
Drug Category: Opiates/Opioids
Topic: Neurobiology
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: A barrier to treating opioid-use disorders is relapse during abstinence, triggered by re-exposure to drug-associated cues. Previous studies have demonstrated that drug-seeking in rats incubates over time during withdrawal (incubation of craving), however the underlying neural substrates are not all known. Here, we examined the role of the orbitofrontal cortex (OFC) in the incubation of craving to oxycodone, a prescription opioid.
Methods: We trained Sprague-Dawley rats to self-administer oxycodone (0.1 mg/kg/infusion) for 10 days and tested them for relapse to oxycodone seeking after 1 or 15 withdrawal days. We measured Fos expression in the OFC after relapse tests on either withdrawal day 1 or 15, compared to no-test controls (n=25). We injected GABAA+GABAB agonists muscimol+baclofen (50+50 ng/0.5 µl/side) or saline into the OFC before relapse tests and examined the effect of reversible inactivation of the OFC on oxycodone seeking on withdrawal day 15 (n=13) or 1 (n=11).
Results: Rats exhibited higher oxycodone seeking on withdrawal day 15 than day 1, demonstrating the incubation of oxycodone craving. Fos expression in the OFC increased in the rats tested for oxycodone seeking on withdrawal day 15, but not day 1, compared to the no-test groups. Inactivation of the OFC by muscimol+baclofen attenuated oxycodone-seeking on withdrawal day 15 ($p=0.02$), but not day 1.
Conclusions: These results demonstrate that neuronal activity in the OFC is associated with incubation of oxycodone craving and the OFC plays a critical role in incubation of oxycodone craving. Future studies will investigate whether the role of the OFC generalizes identify critical projections from the OFC that facilitate oxycodone craving.

Pain

THE SIGMA1 RECEPTOR ANTAGONIST CM304 DOES NOT ENHANCE THE DISCRIMINATIVE STIMULUS EFFECTS OF THE CANNABINOID RECEPTOR AGONIST THC IN RATS

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Abstract Detail: Animal Study
Drug Category: Marijuana/Cannabinoids
Topic: Behavior
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Previous studies conducted in our laboratory have shown that the sigma1 receptor (σ1R) antagonist CM304 may enhance the antinociceptive effects of the cannabinoid agonist, delta (9)-tetrahydrocannabinol (THC) in mice and rats. σ1R antagonists in combination with THC may provide a viable and safe pharmacological alternative to prescription opioids for pain treatment. However, if CM304 also enhances the abuse-related effects of THC, this may limit the therapeutic usefulness of THC and CM304. In this regard, a study was further conducted to determine whether CM304 enhances the effects of THC assessed in a drug discrimination paradigm.
Methods: The present study compared the pharmacological effects of the σ1R antagonist CM304 alone and in combination with THC in Sprague Dawley rats discriminating 3.2 mg/kg THC i.p. from vehicle under a fixed ratio (FR) 10 schedule of food delivery.
Results: THC produced dose-dependent increases in drug-lever responding with an ED50 value of 1.48 mg/kg. The cannabinoid CB1 receptor agonist CP55,940 (0.0056 – 0.56 mg/kg) fully substituted for THC, whereas CM304 (10 – 56 mg/kg) i.p. produced a maximum of 27 % THC-lever responding at 17.8 mg/kg. CM304 at 32 mg/kg decreased response rate to below 25%. No dose of BD1063 (10 – 56 mg/kg, σ1R antagonist), rimonabant, SR144528 (5.6 – 17.8 mg/kg, cannabinoid CB2 receptor antagonist), morphine (1.78 – 32 mg/kg, μ-opioid receptor agonist), or naltrexone (opioid antagonist) produced greater than 30% THC-lever responding. Pretreatment with rimonabant (1.78 mg/kg) produced a rightward shift in the dose-effect function of THC (4.5-fold) and CP55940 (4.5-fold) while pretreatment with CM304 (10 mg/kg), BD1063 (32 mg/kg), SR144528 (5.6 mg/kg), and naltrexone (1 mg/kg) had no significant effect on the THC dose-effect function.
Conclusions: The present results may support the development of a σ1R antagonist as an adjunct to cannabinoids for treatment of acute pain without enhancing the abuse potential of THC.

EXPERIMENTAL PAIN IN DAILY CANNABIS SMOKERS: INFLUENCE OF CANNABIS AND TOBACCO USE

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Abstract Detail: Human
Drug Category: Marijuana/Cannabinoids
Topic: Other
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Over 80% of the 1.2 million registered U.S. medical cannabis patients cite pain as their primary indication. While we have shown sex modulates experimental measures of analgesia following cannabis administration, little is known about the influence of other

individual factors predicting pain response, particularly among cannabis smokers, the population likely to seek a therapeutic use for cannabis.
Methods: This analysis is a subset of data from an ongoing study assessing whether a medication alters the subjective and analgesic effects of cannabis in daily users; placebo medication conditions were analyzed. To control for time since last cannabis exposure, participants smoked six standardized inhalations from cannabis cigarettes (6.5% THC) 105 minutes prior to experimental pain assessment (Cold Pressor Test); our previous data show the analgesic and subjective effects of cannabis dissipates by this timepoint.
Results: To date, data from 14 male daily cannabis smokers (6.9 + 0.5 days/week; 2.9 + 1.5g/day) has been analyzed. Average age was 32.6 + 6.1 years. Six participants also smoked tobacco cigarette, averaging 7.8 + 3.9 cigarettes/day. When controlling for age, the average number of years that participants were daily cannabis smokers (15.5 + 6.8 years) demonstrated moderate positive correlations with pain threshold (19.6 + 15.9 sec; r = 0.41) and tolerance (36.9 + 44.4 sec; r = 0.36). For those who were cigarette smokers, the number of cigarettes smoked per day trended towards a positive correlation with pain threshold (r = 0.3). Other factors (age, amount of cannabis smoked/day) did not correlate with analgesia measures.
Conclusions: These preliminary findings suggest the length of time that someone is a daily cannabis user as well as their cigarette smoking status may positively impact their ability to tolerate pain. A larger sample with a longer time course of data collection is needed to further define these effects.

CORRELATES OF INDICATORS OF POTENTIAL EXTRA-MEDICAL OPIOID USE IN PEOPLE PRESCRIBED OPIOIDS FOR CHRONIC NON-CANCER PAIN

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Behavior
Abstract Category: Original Research
Designation: M.P.H.

Abstract: Aim: The Opioid-Related Behaviors In Treatment (ORBIT) scale is a measure of recent indicators of potential extra-medical opioid use. Indicators of potential extra-medical opioid use are divergent practices among people prescribed opioids that may place them at risk of harm. This study aimed to examine the correlates of indicators of potential extra-medical opioid use in people prescribed opioids for chronic non-cancer pain (CNCP).
Methods: The Pain and Opioids IN Treatment (POINT) study is a prospective cohort study of people prescribed opioids for CNCP in Australia. People prescribed opioids solely for opioid dependence were excluded. This cross-sectional study utilized logistic regression to determine the characteristics associated with reporting any indicators of potential extra-medical opioid use.
Results: Of the 1,505 participants, 38% reported at least one indicator of potential extra-medical opioid use, most commonly asking for an increase in prescribed opioid dose (21%) and early prescription renewal (12%). Indicators of potential extra-medical opioid use were

associated with younger age (Adjusted odds ratio (AOR)=0.98; 95%CI=0.92, 0.99), male sex (AOR=1.53; 95%CI=1.15, 2.04), lifetime pharmaceutical opioid use disorder (AOR=1.87; 95%CI=1.31, 2.66) and lifetime illicit drug use disorder (AOR=1.72; 95%CI=1.18, 2.52).
Conclusions: Over one-third of the POINT cohort reported one or more indicators of potential extra-medical opioid use. Most commonly, these behaviors were asking for an increase in dose and early prescription renewal. Riskier non-adherent behaviors were infrequent. Lifetime substance use disorders were associated indicators of potential extra-medical opioid use, highlighting the importance of clinical monitoring and patient education for this patient group. Longitudinal studies are needed to investigate whether indicators of potential extra-medical opioid use predict opioid use disorders in this population.

STRUCTURE-BASED REFINEMENT OF MPGES-1 INHIBITORS FOR USE AS A NOVEL CLASS OF NON-ADDICTIVE, NON-OPIOID BASED ANALGESICS

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Abstract Detail: Animal Study
Drug Category: Opiates/Opioids
Topic: Chemistry
Abstract Category: Original Research
Designation: B.S.

Abstract: Aim: Pain is one of the most universal symptoms dealt with in medicine. The most commonly used analgesics include opioids and non-steroidal anti-inflammatory drugs (NSAIDs). Currently available NSAIDs posed major gastrointestinal side effects due to the off-target inhibition of prostaglandin synthesis. It is highly desirable to develop safer NSAIDs to prevent use of opioids for chronic pain relief. Previous attempts to create NSAIDs with fewer off-target effects have led to serious cardiovascular events, leaving those who need chronic pain relief with few choices. In previous decades, opioid-based analgesics were popularly used, however the catastrophic rise in opioid use disorders and overdoses have made this class of drugs untenable for use on a chronic basis. One of the most promising candidates for future pain relief pharmaceuticals is the protein microsomal prostaglandin E synthase-1 (mPGES-1), a target downstream from the cyclooxygenase targets of previous NSAIDs. However, there are some substantial roadblocks in creating an inhibitor that allows for testing within established mouse/rat models of pain and related diseases. These issues primarily stem from the incongruities in the binding pocket between the mouse/rat and human mPGES-1, which share few similarities.
Methods: Through the utilization of the protein structures of human and mouse mPGES-1, sites for potential improvement in the ADMET properties of our previously developed compound BAR-002 were identified.
Results: Through our methods of structure-based design, we have synthesized 14 compounds for further testing within in vitro inhibition studies and within in vivo studies of pain and inflammation. These compounds are likely to have improved ADMET properties, as well as increased inhibition of mPGES-1.
Conclusions: Our lab has further optimized a scaffold that utilizes the conserved regions of the two species of proteins, which will allow its use within established mouse/rat models of inflammation and pain and overcome previous development roadblocks.

Phenotyping/Affect/Self-Regulation

INHERENT MOTOR IMPULSIVITY ASSOCIATES WITH SPECIFIC GENE TARGETS IN THE RAT MEDIAL PREFRONTAL CORTEX

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Abstract Detail: Animal Study
Drug Category: Stimulants
Topic: Gene Array/Proteomics
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Identifying targets for neuropharmacological intervention to reduce impulsivity may provide new, transdiagnostic treatment strategies for a myriad of neuropsychiatric diseases. The inability to withhold premature responses (motor impulsivity) reflects failure of "top-down" executive control by the medial prefrontal cortex (mPFC). The present study profiled the complete set of mRNA expressed from genes (transcriptome) in the mPFC of male, outbred rats stably expressing high (HI) or low (LI) motor impulsivity identified in the 1-choice serial reaction time (1-CSRT) task.
Methods: HI and LI rats were defined by the upper and lower quartiles of premature responses in the 1-CSRT task (n=4-6/phenotype), respectively. RNA-sequencing was performed on isolated mPFC homogenate. Gene expression differences in HI vs. LI rats were identified using Fisher's exact test (α=0.1). Functional gene enrichment analyses employed Enrichr, and the ConTra online portal predicted transcription factor binding in silico. Five genes exhibiting the greatest log-fold change difference between HI vs. LI rats were assayed in mPFC homogenates from a second cohort of rats using qRT-PCR.
Results: RNA-sequencing identified n=18 genes as higher in the mPFC of HI vs. LI rats ($p<0.1$). Functional gene enrichment revealed biological processes related to calcium homeostasis ($p<0.05$) and heterotrimeric G protein-coupled receptor signaling pathways ($p< 0.05$) as overrepresented in HI vs. LI rats. Transcription factor enrichment identified SMAD4 ($p<0.05$) as overrepresented while in silico analysis predicted a conserved SMAD binding site within the CACNA1E (Cav2.3) promoter. qRT-PCR analyses confirmed that mRNA expression of CACNA1E as well as LNPEP were higher in the mPFC of HI vs. LI rats ($p<0.05$).
Conclusions: High motor impulsivity associated with high LNPEP and CACNA1E mRNA expression in the mPFC, presenting two novel targets for future impulsivity research. The availability of a Cav2.3¬-knockout mouse model, validated antibody, and peptide antagonist provides an immediate avenue to interrogate Cav2.3 as a target to reduce motor impulsivity.

IMPACT OF STATE ANXIETY SEVERITY ON RETENTION AND PHASE ADVANCEMENT IN AN OUTPATIENT BUPRENORPHINE TREATMENT PROGRAM

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Substance Use Disorder
Abstract Category: Original Research
Designation: M.D.

Abstract: Aim: Although comorbid anxiety is common among buprenorphine patients and may lead to poorer outcomes, data regarding impact of anxiety severity on treatment response is limited. The purpose of this study was to examine prevalence and impact of anxiety severity, as measured by the State-Trait Anxiety Inventory (STAI) form Y-1 scale, on treatment outcomes among outpatient buprenorphine-treated patients.
Methods: Retrospective review of 216 charts of patients consecutively admitted to the University of Arkansas for Medical Sciences outpatient buprenorphine treatment program between January 2012 and February 2017 was conducted. Patients were dichotomized into high and low severity groups based upon a STAI State Anxiety (S-Anxiety) score ≥ 60 and < 60, respectively. Impact of anxiety severity on successful phase advancement and retention during the first 90 days of treatment using logistic regression models.
Results: Fifty of 216 (23%) participants reported high S-Anxiety and had a greater likelihood of phase advancement (OR=2.48, CI= (1.001, 6.17)), but similar likelihood of treatment retention (OR=1.22, CI= (0.49, 2.99)), relative to the low S-Anxiety group.
Conclusions: Contrary to prior reports, buprenorphine patients with higher state anxiety severity demonstrated similar retention and more rapid phase advancement than those with lower state anxiety severity.
To our knowledge this is the first study to quantify current anxiety severity using the STAI State scale and evaluate its impact on treatment outcomes among buprenorphine patients. Results reflect the complexity of conceptualizing anxiety in patients with OUD. Further research is needed to clarify the prevalence and severity of anxiety in individuals with OUD and its impact on buprenorphine treatment outcomes.

SHORT, LONG, AND INTERMITTENT ACCESS MDPV AND COCAINE SELF-ADMINISTRATION IN MALE AND FEMALE RATS

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Abstract Detail: Animal Study
Drug Category: Stimulants
Topic: Behavior
Abstract Category: Original Research
Designation: B.S.

Abstract: Aim: Despite decades of research, the behavioral, pharmacological, and neurobiological determinants of one's vulnerability to develop a substance use disorder are not

well understood. When rats self-administer cocaine under short-access conditions, patterns of drug intake tend to be well-regulated; however, manipulating drug access conditions (e.g., long-access and intermittent-access) can produce neurobiological and behavioral changes thought to be related to addiction. In contrast to cocaine, when rats self-administer the synthetic cathinone 3,4-methylenedioxypyrovalerone (MDPV) under short-access conditions, a subset display high levels of dysregulated drug-taking behavior. However, MDPV has not been studied under extended access conditions. The current studies aimed to test the hypotheses that (1) under short-access conditions, rats self-administering MDPV exhibit higher levels of drug taking, greater rates of responding during periods of signaled drug unavailability, and reduced sensitivity to punishment by foot shock ("addiction-like" behaviors); and (2) long- and intermittent-access to MDPV or cocaine self-administration will result in greater addiction-like behaviors compared to short-access self-administration.
Methods: Ninety-six male and female Sprague Dawley rats self-administered MDPV (0.032 mg/kg/infusion) or cocaine (0.32 mg/kg/infusion) under short-, long-, or intermittent-access conditions prior to evaluating the severity of their addiction-like phenotypes.
Results: Though long- and intermittent-access increase total levels of drug intake and result in repeated bouts of rapid drug intake, respectively, these access conditions did not appear to systematically alter the addiction-like phenotypes of rats self-administering either cocaine or MDPV. However, rats that self-administer MDPV exhibit higher levels of drug taking and greater rates of responding when drug is not available compared to rats self-administering cocaine, regardless of access condition.
Conclusions: These results suggest that the addiction-like phenotype of rats self-administering MDPV may be more robust than the addiction-like phenotypes of rats with a history of self-administering cocaine. Therefore, MDPV self-administration may be a useful method to study individual differences vulnerability to develop substance use disorders.

POSITIVE URGENCY, ALCOHOL CUE SENSITIVITY, AND PROBLEM DRINKING IN YOUNG ADULTS: A MODERATED-MEDIATION ANALYSIS

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Abstract Detail: Human
Drug Category: Alcohol
Topic: Mechanisms of Action
Abstract Category: Original Research
Designation: M.A.

Abstract: Aim: Individuals high in positive urgency (i.e. impulsiveness stemming from high positive mood) may be more sensitive to alcohol cues. This may lead to problem drinking for vulnerable individuals. Our aim was to examine how positive urgency, alcohol cue sensitivity, and consumption patterns concurrently influence the endorsement of alcohol-related problems in a community sample of young adults.
Methods: Participants were 749 young adults enrolled in large, public US mid-western university. The mean age of the sample was 19.6 (SD = 1.72) and 71.3% of participants identified as female. The sample was largely Caucasian (65.5%) and Hispanic/Latinx (22.1%). Participants completed self-report measures online at a single time point.

Results: A moderated-mediation analysis indicated a significant conditional indirect effect. Namely, the relationship between positive urgency and alcohol-related problems was mediated by alcohol cue sensitivity ($B = .486$, $p < .001$), and this relationship was moderated by past 30-day alcohol consumption ($B = .029$, $p < .01$). In other words, individuals with high positive urgency were more sensitive to cues, leading to more impairment as their alcohol consumption increased.
Conclusions: Young adults who drink heavily and display more positive urgency may be at higher risk for problem drinking as a result of cue-elicited cravings and approach motivations. Our results suggest a potential mechanism to inform tailored prevention/intervention plans for alcohol control which incorporate these individual differences.

METABOLIC PROFILE OF RATS BRED FOR INCREASED COCAINE-REINFORCED BEHAVIOR: DECREASED LOCOMOTOR ACTIVITY, INCREASED SLEEP DURATION, AND GREATER ENERGY EXPENDITURE

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Abstract Detail: Animal Study
Drug Category: Stimulants
Topic: Neurobiology
Abstract Category: Original Research
Designation: M.D.

Abstract: Aim: The LS and HS are rat strains selectively bred for Low and High intravenous Self-administration of cocaine. HS (high reward) animals have lower extracellular dopamine, but greater cocaine-induced activation of dopamine receptors in the nucleus accumbens. This study was performed to make detailed measures of metabolism in LS and HS animals exposed to low or high dietary fat.
Methods: Single-housed generation sixteen LS and HS rats were first subjected to a low-fat diet (10 kcal%) over five days with indirect calorimetry performed over 24 hours on the fifth day. Indirect calorimetry measures were repeated on the first and third days of exposure to an alternative high fat diet (45 kcal%). Locomotor activity was detected through infrared beam breaks, and sleep estimated as periods of absent activity for 40 seconds or longer.
Results: HS (high self-administration) rats exhibited lower values for spontaneous locomotor activity and distance traveled, with an elevated sleep duration. When corrected for body weight, energy expenditure was greater in HS rats overall, and during active or quiescent periods. There was no effect of strain on expiration of carbon dioxide or intake of food or water. Exposure to the high-fat diet did not alter metabolic, activity, or sleep measures.
Conclusions: In addition to altered neurotransmitter levels and drug reward, HS rats exhibit different patterns of activity, sleep, and energy expenditure. Spontaneous locomotor activity is decreased in the HS strain with prolonged estimates for sleep duration. Energy expenditure is greater in HS rats during different levels of locomotor activity. The limited time of exposure to dietary interventions may have prevented effects of the high-fat diet. Because altered function of biological rhythms can enhance susceptibility to drug reward in other animal models, altered rhythms may also contribute to reward behavior in HS rats.

Polysubstance Abuse

AMPHETAMINE TYPE STIMULANT USE AMONG EMERGENCY DEPARTMENT PATIENTS WITH OPIOID USE DISORDER

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Abstract Detail: Human
Drug Category: Opiates/Opioids
Topic: Substance Use Disorder
Abstract Category: Original Research
Designation: M.D.

Abstract: Aim: Use of amphetamine type stimulants (ATS) can negatively impact treatment outcomes among individuals with opioid use disorder (OUD) and increase the risk of overdose and medical complications. We compared the sociodemographic and clinical features of Emergency Department (ED) patients with OUD who use ATS as compared to those who don't.
Methods: Sociodemographic and clinical data obtained during the enrollment period between 2/2017 and 1/2019 of a study evaluating the implementation of OUD treatment initiation in emergency departments (EDs) in Baltimore, MD, New York, NY, Cincinnati, OH, and Seattle, WA (NIDA CTN 0069) was used in exploratory analyses. Urine samples collected from study participants meeting DSM-V criteria for OUD were tested for methamphetamine and amphetamine metabolites using instant immunoassay tests. Samples testing positive for methamphetamine, amphetamine, or both were classified at ATS positive.
Results: Among the study sample 150/396 (38%) were ATS positive. ATS positive as compared to ATS negative participants were more likely to be from the Midwest and West Coast EDs; younger: 36 (10) vs. 40 (12) years; a higher proportion of them were white: 104/169 (69%) vs. 114/246 (46%); a higher proportion had unstable housing: 101/150 (67%) vs. 121/246 (49%); a higher proportion presented at ED with opioid overdose: 32/150 (23%) vs. 33/246 (13%); and a higher proportion reported injecting drugs in the prior month: 118/150 (79%) vs. 115/245 (47%) (all $p<0.05$).
Conclusions: ATS use is prevalent among OUD individuals presenting to EDs in the Midwest and West Coast and was associated with specific sociodemographic and clinical features. Given the impact of ATS use on health and OUD treatment efforts, it is important to determine potential impact of ATS use on OUD treatment initiation and to develop ED-based screening and referral protocols for ATS using individuals utilizing urine tests and self-report.

GABAA RECEPTOR SUBTYPES AND THE REINFORCING EFFECTS OF BENZODIAZEPINES IN OPIOID-EXPERIENCED RHESUS MONKEYS

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Abstract Detail: Animal Study
Drug Category: Opiates/Opioids
Topic: Behavior
Abstract Category: Original Research
Designation: Ph.D.

Abstract: Aim: Opioid-use disorder is associated with a high degree of co-abuse with benzodiazepines, which complicates treatment and increases risk of overdose deaths. While the mechanisms underlying the co-abuse of opioids and benzodiazepines remain unknown, α1 subunit-containing GABAA (α1GABAA) receptors seem to have a critical role in the reinforcing effects of benzodiazepine-type compounds in monkeys with a history of benzodiazepine and stimulant self-administration. The aim of the present study was to investigate the extent to which a compound lacking activity at α1GABAA receptors functioned as a reinforcer in monkeys trained to self-administer the opioid remifentanil, and whether that drug is more or less robust as a reinforcer compared with full and partial GABAA receptor positive allosteric modulators (modulators).
Methods: We investigated the reinforcing effects of L-838,417, a selective compound that has partial intrinsic efficacy at α2, α3, and α5 subunit-containing GABAA receptors, but lacks efficacy at α1GABAA receptors (α1-sparing compound). Its reinforcing effects were compared with those of the non-selective benzodiazepine receptor partial modulator MRK-696, and non-selective benzodiazepine receptor full modulators, triazolam and lorazepam, in rhesus monkeys (n=3) trained to self-administer remifentanil under a progressive-ratio schedule of intravenous drug injection. Data were analyzed using repeated-measures ANOVA and Bonferroni post-hoc tests.
Results: Neither the partial modulator nor the α1-sparing compound were self-administered above vehicle levels. The full modulators triazolam ($p<0.05$) and lorazepam ($p<0.05$) were self-administered significantly above vehicle levels, albeit at lower levels than remifentanil.
Conclusions: In contrast to monkeys with benzodiazepine or stimulant self-administration histories, α1GABAA receptors do not seem to have a role in the reinforcing effects of benzodiazepines in opioid-experienced monkeys. Instead, high intrinsic efficacy at all benzodiazepine-sensitive GABAA receptors is necessary for reinforcing effects of benzodiazepine-type compounds in opioid-experienced rhesus monkeys.

ON DAYS WHEN CANNABIS IS CONSUMED, HOW DOES OPIOID USE CHANGE?

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Abstract Detail: Human
Drug Category: Polydrug (i.e. Use of more than one drug combination)
Topic: Drug Interactions
Abstract Category: Original Research
Designation: B.Sc.

Abstract: Aim: Prospectively evaluate how cannabis consumption changes the probability of opioid use in a given day, and whether this relationship differs between people with and without pain.

Methods: As part of a larger study, individuals with past-month opioid use (N=211) were recruited via ads and social media in a research setting in the New York City metropolitan medical area, and from an inpatient rehabilitation unit. Participants were interviewed at baseline, then answered daily questions about their substance use for the following 90 days via cellphone. Cannabis use was defined as responding "yes" to use of marijuana. Opioid use was defined as responding "yes" to use of heroin and/or non-medical prescription opioid use. Baseline covariates included gender, age, ethnicity, marital status, employment status, recruitment setting, opioid type, and pain.
A logistic mixed model, with a random intercept for participant and random slope for time was used. We assessed (1) the crude and adjusted associations between cannabis and opioid use, and (2) whether this association differed between people with and without pain.

Results: In unadjusted analyses, cannabis use was associated with a 100% increase in the odds of opioid use (OR=2.00, 95% CI = 1.54-2.59, p<.0001), while in adjusted analyses, cannabis use was associated with an 86% increase in the odds of opioid use (OR=1.86, 95% CI= 1.44-2.41, p<.0001). The interaction term, pain by cannabis use, was not statistically significant (F=1.55, DF=1, p=.23).
Conclusions: For a given individual, cannabis use was positively associated with opioid use in a given day. This relationship did not differ between people with and without pain, suggesting that cannabis is generally not substituted for illicit opioids, even for individuals who report chronic pain. Increasing access to marijuana may not aid individuals in limiting their opioid use.