Sunday, June 16, 2024

ORAL SESSION: FROM LAB RATS TO SMOKESTACKS: PRECLINICAL INSIGHTS INTO NICOTINE ADDICTION

Contraceptive Hormone Ethinyl Estradiol Modulates the Reward-Enhancing but not the Primary Reinforcing Effects of Nicotine in Ovary-Intact Female Sprague-Dawley Rats

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Drug Category: Nicotine/Tobacco
Topic: Behavioral Pharmacology
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research

Aim: Hormonal contraceptives are taken by roughly 50% of premenopausal smokers. Many hormonal contraceptives contain a synthetic estrogen (e.g., ethinyl estradiol/EE). EE heightens nicotine/smoking reward. However, whether this heightened effect reflects alteration in nicotine reinforcement or enhancement by nicotine of co-occurring reinforcers is unknown. This latter reward-enhancement effect is modeled in rats by measuring responding maintained by nicotine alone or with a reinforcing visual stimulus (VS). Nicotine self-administration is dramatically increased by co-occurrence with the VS. We sought to examine the effects of EE on nicotine reinforcement and reward-enhancement in an intravenous self-administration task.
Methods: Ninety-two ovary-intact female Sprague-Dawley rats were assigned to receive pre-session injections of EE (vehicle, 0.125, or 0.18 mcg/day) and self-administer 0.03 or 0.06 mg/kg/infusion nicotine or saline during two, ten-session phases. Rats started in an Infusion Only phase, responding only for their assigned infusion. Rats then progressed to the Infusion+VS Phase, now responding for their assigned infusion and a 30-second VS. We hypothesized that contraceptive hormones would influence nicotine self-administration during the Infusion+VS phase, but not the Infusion Only phase. We conducted a three-way mixed ANOVA for each phase examining Session, EE Dose, and Nicotine Dose.
Results: For the Infusion Only phase, there were no effects of EE. Rats responded more for 0.06 mg/kg/inf nicotine than saline ($p<.001$), but not 0.03 mg/kg/inf nicotine ($p=0.052$). For the Infusion+VS Phase, EE Dose influenced nicotine-maintained responding such that vehicle rats responded more for 0.03 mg/kg/inf nicotine than saline or 0.06 mg/kg/inf nicotine (ps LESS THAN .001), while 0.125 mcg/day EE rats responded more for 0.03 and 0.06 nicotine mg/kg/inf than saline ($ps\leq.023$). Nicotine-maintained responding was not different from saline for 0.18 mcg/day EE rats ($ps\geq.850$).
Conclusions: In conclusion, EE impacted nicotine reward-enhancement but not primary reinforcement. These results support investigation of novel nicotine cessation therapeutics for women taking EE-containing contraceptives.
Financial Support: Research supported by NIH R01-DA034389.

Effects of Menstrual Cycle Phase on the Neural Correlates of Electronic Cigarette Versus Tobacco Use

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Drug Category: Nicotine/Tobacco
Topic: Imaging
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research

Aim: Estradiol and progesterone are neuroactive steroid hormones that modulate the menstrual cycle (MC). These ovarian hormones affect neural activity in individuals who use tobacco,and contribute to the significant

sex differences seen in nicotine dependence. This study aims to investigate the effects of MC phase on neural activity in women who vape nicotine (NV) compared to women who smoke tobacco (TS).
Methods: Three groups (n=20/group): (1) NV; (2) TS; (3) healthy controls (HC). All groups complete 2 MRI scanning sessions while 12-h nicotine abstinent [once during late-FP (high estradiol), once during mid-LP (high progesterone)]. A cue-reactivity task with validated vaping, smoking, and neutral image cues is presented in block design. fMRI data is analyzed by fitting a general linear model to the data time-series at every voxel across the brain and at ROIs. Only female participants are included.
Results: 17 NV, 18 TS, and 16 HC have enrolled in the study to date. NV are: younger overall than TS group (22.90 ± 3.31 vs 24.67 ± 3.73); were older initiation of vaping (19.90 ± 2.57) compared to smoking in the TS group (16.94 ± 2.33); and had a higher score on the Fagerstorm Test for Nicotine Dependence for e-cigarettes (e-FTND) (4.05 ± 2.64) compared to FTND score in the TS group (2.17 ± 2.12). MRI findings for the fully recruited sample will be presented.
Conclusions: This is the first study to examine how MC phase and ovarian hormones affect neural activity in NV. Findings will help develop and optimize nicotine-cessation interventions specific to women.
Financial Support: Womenmind Grant from the Centre for Addiction and Mental Health

Nicotine Use Sex-Specifically Dysregulates Microglial Structure Within the Nucleus Accumbens

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Drug Category: Nicotine/Tobacco
Topic: Behavior
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research
Aim: Nicotine use alters reward pathway neuroimmune signaling, including increased pro-inflammatory cytokine production within the nucleus accumbens core (NAcore). Microglia are resident brain immune cells, and nicotine withdrawal induces NAcore microglial reactivity. The NAcore has been heavily implicated in addiction processes, including nicotine use; however, most studies have evaluated nicotine neurobiology exclusively in males, with biological sex not considered. This is an important factor to consider given that neuroimmune signaling and nicotine use are regulated by sex steroid hormones. Thus, the current study evaluated nicotine-induced NAcore microglia reactivity following self-administration (SA) as a function of biological sex.
Methods: 44 male and female Long Evans rats underwent nicotine (0.06 mg/kg/infusion) or saline SA for 8 sessions. NAcore tissue was then dissected for microglial morphometrics using the automated analysis program 3DMorph. Data were analyzed via linear mixed effects (LME) modeling with Tukey's post-hocs or linear regressions for correlations of microglia outcomes with nicotine consumption.
Results: There were main effects of session and sex and a sex x session interaction in nicotine consumption (p's<0.05) indicating that males consumed more nicotine than females across sessions. Microglial morphometric analysis revealed that nicotine use significantly reduced minimum and maximum branch lengths as well as number of endpoints and number of branchpoints only in males (p's<0.05), indicating greater nicotine-induced NAcore microglial reactivity in males than females. In males, positive correlations were found between total amount of nicotine consumed and the average number of endpoints ($R2=0.99$, $p<0.0001$) and average branchlength ($R2=0.95$, $p<0.0001$), indicating that greater nicotine use increases microglial cellular complexity.
Conclusions: These results indicate that sex-specific dysregulations in NAcore neuroimmune signaling occur following volitional nicotine SA, with males being more susceptible than females to nicotine-induced dysregulations in microglia structure. Further studies are needed to determine if steroid hormones contribute to protection against nicotine-induced neuroimmune dysregulations in females.
Financial Support: This work was funded by grants DA046526, DA058933, DA049130, and DA055879 (to CDG).

Effects of Cigarette and E-Cigarette Flavor Restrictions on Substitution in the Experimental Tobacco Marketplace

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Drug Category: Nicotine/Tobacco
Topic: Policy
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research

Aim: Government regulations can control the design features of tobacco products, including flavors. Understanding how these flavors affect users' choices can help determine the impact of such policies. This study investigated how the availability of e-cigarette and cigarette flavors affects consumers' purchases in the Experimental Tobacco Marketplace (ETM), a simulated environment designed to mimic real-world tobacco purchasing behavior.

Methods: In a within-subject design, 25 individuals who smoke menthol cigarettes completed purchasing trials with increasing cigarette prices in the ETM under four different scenarios: a) cigarette flavor restricted and e-cigarette flavor restricted, b) cigarette flavor unrestricted and e-cigarette flavor restricted, c) cigarette flavor restricted and e-cigarette flavor unrestricted, d) cigarette flavor unrestricted and e-cigarette flavor unrestricted.

Results: The results showed that 1) cigarette flavor restriction decreased cigarette demand compared to when cigarette flavor was unrestricted ($p<0.001$), 2) e-cigarette flavor restriction decreased willingness to purchase e-cigarettes ($p=0.011$), 3) cigarette flavor restriction increased e-cigarette substitution compared to when cigarette flavor was unrestricted ($p<0.028$) among those who purchased e-cigarettes, 4) e-cigarette flavor restriction resulted in greater Nicotine Replacement Therapy (NRT) substitution among those who purchased NRTs compared to when e-cigarette flavors were unrestricted ($p<0.013$).

Conclusions: Our findings suggest that restricted cigarette flavor, compared to unrestricted, significantly decreases cigarette demand and increases e-cigarette substitution, pointing to the potential effectiveness of this regulatory intervention in transitioning individuals from menthol cigarettes to alternative products. Additionally, restrictions on e-cigarette flavor decreased substitution for e-cigarette and increased substitution for NRT. As policymakers deliberate on strategies to address tobacco-related public health concerns, our study underscores the importance of comprehensively evaluating the broader implications of flavor restrictions on consumers' preferences.

Financial Support: Supported by the National Cancer Institute at the National Institutes of Health (grant number 5P01CA200512) and the Fralin Biomedical Research Institute at Virginia Tech Carilion.

ORAL SESSION: AMYGDALA ACTIVITY AND SUDS - DEEP IN THE FEELS

The Role of the Basolateral Amygdala in Reward-Seeking Evoked by Sucrose-Predictive Discriminative and Conditioned Stimuli in Female and Male Rats

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Drug Category: Other, Natural reward
Topic: Neurobiology/Neuroscience
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research

Aim: Environmental cues that predict reward, such as conditioned stimuli (CSs) and discriminative stimuli (DSs), are essential for survival. However, such reward-cues can also contribute to maladaptive reward-seeking as in addiction, gambling, and eating disorders. The basolateral amygdala (BLA) mediates CS-driven reward-seeking; however, little is known about the BLA's role in behaviour under the control of DSs. Here, we used optogenetic and pharmacological techniques to determine the role of the BLA in reward-seeking evoked by a reward-associated DS and CS.

Methods: Female and male Sprague-Dawley rats were trained to discriminate between a DS+ (discrete light) during which lever presses produced sucrose paired with a 5-s CS+ (light+tone), and a DS- (different discrete light) that signaled sucrose unavailability. We then assessed the effects of these cues on sucrose-seeking behaviour, and their conditioned reinforcing properties.
Results: Presentations of the DS+ and CS+, but not the DS-, evoked high levels of sucrose-seeking (pressing the previously active lever), with the DS+ producing the highest rates of responding. In a separate test, rats showed similar rates of lever pressing reinforced by the DS+ or CS+ (without sucrose), suggesting that the two cues acquired comparable conditioned reinforcing properties. The two sexes showed similar response profiles across the two different tests. Cue-paired photostimulation (465-nm, 20-Hz, 10-mW, 5 s) of ChR2-eYFP expressing BLA neurons did not impact cue-triggered sucrose-seeking regardless of cue type; however, in both females and males, photostimulation did invigorate responding to obtain DS+ presentations during conditioned reinforcement tests. Administering the mGluR2/3 agonist LY379268 into the BLA reduced both sucrose-seeking triggered by the DS+ and CS+ and responding for these cues during conditioned reinforcement tests and did so similarly across the sexes.

Conclusions: Thus, across the sexes, the BLA mediates reward-seeking controlled by both CSs and DSs, implicating BLA neurons in distinct forms of cue-controlled reward-seeking behaviour.
Financial Support: NSERC Discovery Grant (Anna Samaha); NSERC Postdoctoral Fellowship (Mandy R. LeCocq)

Role of Corticotrophin-Releasing Factor in the Central Amygdala on Enhancement of Memory Consolidation by Unconditioned and Conditioned Heroin Withdrawal

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Drug Category: Opiates/Opioids
Topic: Neurobiology/Neuroscience
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research
Aim: Recent preclinical evidence suggests that unconditioned and conditioned opioid withdrawal could promote the learning of addictive behaviours by facilitating memory consolidation. To further understand the neurobiology of the memory-enhancing effects of unconditioned and conditioned opioid withdrawal, the current study focused on corticotrophin-releasing factor (CRF) in the central amygdala (CEA) because of their known role in withdrawal and memory consolidation.
Methods: Male Sprague-Dawley rats (N = 38) with sham surgery (No US group) or implanted (SC) with osmotic mini-pumps releasing 3.5 mg/kg/day heroin (US group) received 3 mg/kg naloxone (NLX) to precipitate withdrawal immediately post-training (i.e., during the period of memory consolidation) and were tested 72 hr later for object recognition memory. In the conditioned withdrawal study, rats were pre-treated with heroin (1 mg/kg x 2 injections SC) and then administered 3 mg/kg NLX (SC) prior to confinement in one compartment (CS+) of a place conditioning apparatus or vehicle prior to confinement in the alternative compartment (CS-). For memory testing, these rats were exposed to the CS+ or the CS- immediately post-training and then tested for object memory 72 hours later. In both studies, rats received intra-CeA bilateral infusions of the CRF1 receptor antagonist Antalarmin (ANT; 0–2 ug/side) immediately prior to NLX or exposure to the NLX-paired CS+.
Results: Intra-CeA infusions of ANT blocked the enhancement of object memory consolidation by both NLX-precipitated withdrawal [$p = 0.002$] and by conditioned withdrawal [$p = 0.017$].
Conclusions: These studies suggest that pharmacological and psychological opiate withdrawal influence memory storage through CRF neurotransmission in the CEA.
Financial Support: Research is supported by the Natural Sciences and Engineering Research Council of Canada.

Individualized Targeting of Frontolimbic Networks in People with Methamphetamine Use Disorder: Multi Target Optimization Using Neuroimaging

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Drug Category: Stimulants
Topic: Imaging
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research

Aim: Substance Use Disorder (SUD) presents a significant global health challenge, necessitating innovative interventions for its treatment, including noninvasive brain stimulation (NIBS) methods. However, target selection for SUD treatment, particularly for transcranial stimulation methods, like TMS, remains challenging. Emerging evidence underscores the crucial role of cortico-subcortical connections, mainly, fronto-limbic in driving addictive behaviors. These connections can be targeted with brain stimulation interventions. Previous NIBS studies for SUDs have mainly targeted the DLPFC, but recent evidence suggests that the frontopolar cortex might play a mediating role in the observed clinical effects of NIBS protocols, even when not directly stimulated. However, the distinct while interacting roles of DLPFC and frontopolar cortex have not been thoroughly explored as dual targets. In this study, we investigated the interactions between frontopolar, DLPFC, and amygdala during drug cue exposure, at both individual and group levels, indicating that targeting DLPFC and frontopolar cortex separately may have opposite or augmenting effects on subcortical areas and cue-induced craving.

Methods: fMRI drug cue reactivity data were collected from 60 male participants (mean±SD=35.86±8.47 years) with methamphetamine use disorders as part of a pre-registered trial (NCT03382379). Prior to and immediately after drug cue exposure, cue-induced cravings were assessed using VAS scores. Averaged cue reactivity was extracted from all brain sub-regions using Brainnetome atlas parcellation. The subcortical brain region exhibiting the highest functional reactivity to drug cues was selected as the seed region (amygdala) for further seed-to-whole brain psychophysiological interaction (PPI) analysis. To demonstrate inter-individual variability in fronto-limbic connections, Brodmann's masks that showed overlap with seed-to-whole brain clusters in prefrontal cortex were extracted. The location and strength of the most positive connection between the subcortical seed region (amygdala) and the mask that showed increased PPI connectivity, as well as the most negative connection between the subcortical seed region and the cluster that showed decreased PPI connectivity during drug cue exposure, were calculated. Correlations between ROI-to-ROI PPI connectivity and changes in craving scores were also assessed.

Results: After drug cue exposure, craving scores exhibited a significant increase (P=0.002). Among the subcortical regions, the left medial amygdala was chosen as the seed region due to its highest FDCR (0.31±0.29). Amygdala-to-whole brain PPI revealed two clusters, one in the frontopolar area with increased PPI connection (size:863, center:[20,44,30],P-FDR:0.0007, Hedge's g=0.1, overlap with Brodmann area 10), the other one in DLPFC (size: 42, center:[44,38,6],P-FDR:0.001, Hedge's g=0.15, overlap with Brodmann area 9,46). Amygdala-to-DLPFC mask PPI analysis revealed notable inter-individual variability in terms of both the location ([29.5,49.9,22.1]±[16.2,10.1,15.7]) and strength (-1.2±0.6) of the most negative PPI connections. Regarding the amygdala-to-frontopolar mask PPI connectivity, inter-individual variabilities were found in both location ([0.2,61.8,3.9]±[25.7,6.1,10.2]) and strength (1.05±0.45). We also found variations in terms of connectivity strength between individualized frontopolar and DLPFC locations ranging from -0.98 to 1.2. Furthermore, a significant positive correlation (R=0.27,P=0.03) was found between craving scores following drug cue exposure and frontopolar-amygdala PPI connectivity, while the correlation with DLPFC-amygdala connectivity was negative (R=-0.15, P=0.2).

Conclusions: Our study reveals significant differences in brain connectivity patterns between the frontopolar-amygdala and DLPFC-amygdala connections during drug cue exposure. The increased PPI and positive correlation observed in the frontopolar-amygdala connection suggest its involvement in drug-craving responses through bottom-up processing. Conversely, the DLPFC-amygdala connection exhibits decreased PPI connectivity and a negative correlation, indicating its role in top-down control by exerting inhibitory effects on both frontopolar and Limbic areas. To effectively control cue-induced craving, inhibiting the frontopolar-Limbic connection while exciting the DLPFC may be a promising approach. Prior studies have demonstrated the efficacy of inhibitory TMS (cTBS) over frontopolar and excitatory TMS (rTMS) over

DLPFC in this context. Therefore, when designing brain stimulation studies, careful consideration of brain connections is vital in determining whether to excite or inhibit specific brain regions. Furthermore, the considerable inter-individual variability in the location and strength of cortico-subcortical connections emphasizes the need for personalized target selection to optimize the modulation of relevant brain circuits. Our pipeline suggests fMRI-informed targets that help to achieve this personalized stimulation.
Financial Support: Medical Discovery Team on Addiction, University of Minnesota

The Effect of Oxytocin and Social Support on Social Reward in Cocaine Use Disorder

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Drug Category: Stimulants
Topic: Neurobiology/Neuroscience
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research
Aim: Social functioning contributes to the onset, development, and treatment of addiction, including cocaine use disorder (CUD). Individuals with CUD can experience isolation and altered physiological and subjective responses toward favorable social interactions. Oxytocin (OT), a peptide involved in social bonding, may counteract neurocognitive changes associated with social reward in CUD. The current study examined how OT versus placebo potentiated amygdala (AMY) connectivity with the prefrontal cortex in response to implicit positive valence face cues among individuals with (CUD+) or without CUD (CUD-). Further, moderation of these circuits' potentiation by perceived social support (pSS) was examined.
Methods: CUD+ (N=51) and CUD- (N=47) individuals received intranasal OT (24IU) or placebo preceding a functional magnetic resonance imaging (fMRI) scan with an implicit facial affect task. Functional connectivity was assessed with psychophysiological interaction using the bilateral AMY as seeds. Contrasts between emotions involving the happy face cue with respect to treatment (TX; OT vs placebo) and diagnosis (DX; CUD+ vs CUD-) were examined at the voxel-level. Regions that showed TX and/or DX effects were subject to post-hoc general linear models to probe moderation by pSS alongside relevant covariates.
Results: Voxel-wise analyses indicated a TX effect with OT reducing right AMY-right superior frontal gyrus (SFG) coupling. A post-hoc interaction between DX x TX x pSS was also observed (X^2=4.2, p=.04). Subsequent analysis of TX x pSS conducted for each DX revealed OT was associated with negative connectivity in CUD-, amplified by lower levels of pSS. Conversely, OT's effect was not modulated by pSS in CUD+ and even TX alone did not survive following inclusion of covariates.
Conclusions: pSS modulates OT's effect on AMY-SFG connectivity for social reward in CUD-. Neither OT nor its interaction with pSS are associated with social reward in CUD+. Future research should explore alternatives for enhancing social reward in CUD+.
Financial Support: R01DA037968, K24DA038240, U54DA016511, UL1TR001450

ORAL SESSION: ADVANCING DRUG USE PREVENTION ACROSS THE CONTINUUM

Five-Year Substance Use Disorder Outcomes Following School-Based Cognitive Behavioural Interventions that Target Internalizing and Externalizing Traits: A Cluster Randomized Trial

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Drug Category: Polydrug (i.e. concurrent use two or more drugs)
Topic: Prevention
Abstract Detail: Clinical - Experimental

Abstract Category: Original Research
Aim: Upstream solutions that help to prevent transition to Substance Use Disorder (SUD) are desperately needed, considering the scale and severity of the addiction and overdose crisis in North America. The current study investigates the five-year SUD outcomes of a selective drug and alcohol prevention program that targets personality risk factors for adolescent substance misuse.
Methods: Design and setting: The CoVenture Trial (NCT01655615) is a cluster randomized trial involving 31 secondary high schools from the greater Montreal area agreeing to conduct annual health behaviour surveys for five years on the entire 7th Grade cohort of consenting students enrolled at the school in 2012 or 2013 (2). Half of all schools were randomly assigned to be trained to deliver the personality-targeted Preventure program to all eligible youth. Primary outcomes focus on intent to treat sample of 7th grade students who scored one standard deviation above the school mean on one of the four Substance Use Risk Personality Scale (SURPS, 3) subscales assessing impulsivity, sensation seeking, anxiety sensitivity or hopelessness. This translated to 45% of the grade being eligible for the program. The Preventure Program was delivered to all students while in the 7th grade. It is a brief (2-session) cognitive-behavioural intervention that is delivered in a personality-matched fashion aimed at helping youth who report high personality scores to develop personality-specific cognitive and behavioural strategies to better manage the target personality trait.

Mixed effects multi-level Bayesian models were used to estimate the effect of the intervention on the year-by-year change in diagnoses of emerging or obvious SUD, as assessed by the Detection of Alcohol and Drug Problems in Adolescents questionnaire (DepAdo, 41,43), which is used in Quebec high schools to screen for and intervene on students' emerging and obvious SUDs.

Results: Analysis on annual outcomes over five years indicated a time by intervention effects, which when controlling for baseline demographic and pre-intervention differences in SUD, revealed a greater increase in emerging and obvious SUD over time for the control group (b=1.295, CI= [1.137-1.460])
relative to the intervention group (b=-0.702, CI= -0.916, -0.487]). These group differences were reliably non-zero with 95% confidence at the fourth and fifth year of assessment. Sensitivity analysis controlling for missingness (Inverse Probability of Weights, IPW) also revealed reliable group differences with 95% confidence. There was also a preliminary sign that the intervention was associated with prevention of prescription drug use over the four follow-up sessions (b=-.004, SE=0.002, CI= [-.008,0.000]).

Conclusions: While personality-targeted brief cognitive behavioural interventions have been consistently shown to reduce and delay substance use and mental health symptoms in adolescents, this study showed for the first time that the intervention approach might protect against longer-term development of SUD, including prescription drug misuse, in youth who report personality risk factors.
Financial Support: Canadian Institute for Health Research

Massachusetts School-Based Health Center Providers' Beliefs and Attitudes About Overdose Prevention

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Drug Category: Opiates/Opioids
Topic: Prevention, Youth Opioid Overdose Prevention education in School-based Health centers
Abstract Detail: Other
Abstract Category: Original Research
Aim: To examine Massachusetts School-Based Health Center (SBHC) practitioners' beliefs and attitudes on providing overdose prevention education and medications for opioid use disorder (MOUD) in SBHCs.
Methods: We conducted a qualitative study of SBHC staff who attended a two-day adolescent focused training. The interview guide included four domains: 1) prior substance use education, 2) overdose prevention and reversal, 3) prescribing MOUD, and 4) family involvement. After professional transcription of the recorded interviews, we conducted a thematic analysis using a hybrid deductive and inductive approach.

Results: We interviewed 13 Massachusetts school SBHC providers: 11 female, two male, ten white, one Latinx, and two Black. Six were medical providers and seven behavioral health providers. We identified four themes. First, participants reported minimal training on substance use and overdose prevention,and wanted more adolescent-focused training. Second, they shared a concern that current screening tools do not identify youth at risk for overdose. Third, participants advocated to apply harm reduction strategies when working with youth who use substances. Finally, participants believed that the SBHC teams, primary care providers, school staff, and students' families needed improved care coordination to address adolescent substance use.
Conclusions: Opioid overdose among youth is increasing. There is an urgent need for innovative approaches for effective overdose prevention strategies for them. This study found that SBHC staff are familiar with providing harm reduction education for substance use and are well positioned to provide overdose education to youth. There are however challenging system level barriers to implement MOUD. Future work could focus on development and implementation of overdose prevention interventions in SBHC.
Financial Support: The study funded by Becca Schmill Foundation, and I am supported by NIDA R25 (RAMS).

Development of a Digital Neuroscience-Based Cognitive Resilience Training Program for Substance Use Prevention

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Drug Category: Other, Substance use prevention targeting all drug categories
Topic: Prevention
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research
Aim: Most of the revolutionary advances in understanding the neurobiological basis of addiction have not been translated into prevention and intervention programs for substance use disorders (SUD). To address this gap, we recently developed a Neuroscience-Informed Psycho-Educational (NIPE) program for adolescents and young adults, whose goal is to enhance metacognitive awareness, build cognitive resilience, and promote the use of specific neurocognitive skills to prevent or reduce substance misuse. The mobile app-based program consists of four self-administered 20 to 30 minutes-long sessions, focusing on specific neurocognitive functions implicated in SUD: (1) Attention, (2) Memory, (3) Cognitive Flexibility/Inhibitory Control; and (4) Decision-Making/Incentive Salience. The program incorporates neurocognitive games, videos, animations, and cartoons based on real-life scenarios, and provides interactive psychoeducation on key neurocognitive functions implicated in SUD and cognitive components of resilience.
Methods: We conducted a pilot study testing the feasibility of delivering the program to undergraduate students. Consenting participants were invited to complete a pre-intervention risk-assessment survey, the 4 app-based intervention sessions, and a post-intervention online survey, which also included feedback about the intervention. All study components were administered online. Ninety participants showed interest in the study, of whom 85 completed the pre-intervention survey and 67 completed all intervention sessions and the post-intervention survey.
Results: Results support the feasibility of administering the program to college students. Student feedback reveals high acceptance and satisfaction with the program, including the length and number of sessions. From the different intervention components, the neurocognitive games were liked the most and the brain training strategies were liked the least. Preliminary results from pre- and post-intervention comparisons show increase in metacognitive awareness, coupled with reductions in depression, anxiety, intentions to get drunk in the next 30 days, as well as in self-reported deficits in executive function and delay discounting.
Conclusions: These preliminary results provide evidence for feasibility and will be used to revise the intervention and conduct a randomized controlled trial (RCT) to evaluate its efficacy.
Financial Support: This project was supported, in part, by CTSA award UL1TR002649 from the National Center for Advancing Translational Sciences and the CCTR Endowment Fund of Virginia Commonwealth University, R01DA021421 award from the National Institute on Drug Abuse and the Fogarty International Center, and R01DA058038 award from the National Institute on Drug Abuse.

Developing a Tool to Assess the Risk of Transitioning From Occasional Opioid Use to Opioid Use Disorder

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

Aim: Despite widespread opioid use at a societal level, only a minority of individuals exposed to opiates progress to opioid use disorder (OUD). Can individuals predisposed to developing OUD upon opiate exposure be identified before first use? In this initial study, our objective was to develop an instrument that could accurately differentiate cohorts with different opiate-use statuses, laying the groundwork for predictively differentiating those at risk of OUD in a comprehensive, large-scale longitudinal study.
Methods: We collected data for 27 well-validated instruments (550 individual questions) covering four risk domains: Overall Life Quality, Opioid-Induced Hedonic Experience, Genetic Predisposition, and Psychological Predisposition. We had 150 participants equally divided between three matched cohorts: those with a history of OUD, those exposed to opiates but with no history of OUD, and a control cohort with no exposure. Employing a two-step modeling process, we applied dimension reduction methods to our dataset comprising 550 data points per participant,and utilized linear discriminant analysis for classification. Our goal was to identify the minimal number of questions required to classify these cohorts.
Results: We identified just 10-25 questions extracted from the 27 instruments that were, when combined together, able to separate the three cohorts with reasonable efficiency. Questions related to lifetime stress, coping, social support, reward responsiveness, and impulsivity emerged as influential in separating the cohorts. Accuracy rates were in the x%-y% range for the training, and u%-v% range for the testing data, for these 10-25 questions.
Conclusions: Using a between-subjects approach as an initial step, we were able to identify opiate-use status with high precision. This lays the groundwork for employing these features in a longitudinal predictive study. Such an approach holds promise for accurately identifying individuals at risk for OUD prior to first exposure, thereby contributing to the advancement of early intervention strategies.
Financial Support: *Supported by Behavioral Sciences Training in Drug Use Research
* Co-Investigator Paul Glimcher declares a potential conflict of interest. He holds significant stock in DataCubed Health which provided their app pro bono for this study.

ORAL SESSION: OUCH!!! PASS THE CANNABIS

Cannabidiol (CBD) Co-Administration Alters Delta-9-Tetrahydrocannabinol (THC) Antinociception in the Carrageenan Rat Model of Acute Inflammatory Pain

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Drug Category: Cannabis/Cannabinoids
Topic: Behavioral Pharmacology
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research

Aim: Pain relief is the most frequent use for medical cannabis. Some pain patients also substitute cannabis for prescription opioids. Cannabis products being used are delta-9-tetrahydrocannabinol (THC) or cannabidiol (CBD) dominant with variable THC:CBD ratios. Some data suggests that THC and CBD produce analgesia and reduce inflammation. CBD may also augment the therapeutic and/or mitigate the adverse effects of THC. This study tested the anti-nociceptive and anti-inflammatory effects of THC and CBD, alone or combined in different ratios, using a rat model of inflammatory pain.

Methods: Inflammatory pain was induced in adult Sprague Dawley rats via an intraplantar λ-Carrageenan injection in the rat hind paw. Rat treatment dose groups (n = 8-12 per sex/group) were orally administered sesame oil vehicle (control), THC (1, 3 mg/kg) CBD (10, 30 mg/kg), or THC+CBD dose combinations under blinded conditions. Drugs were administered 1 hour prior to λ-Carrageenan. Pain and edema measurements were conducted at baseline, 1, 3 and 5 hours post λ-Carrageenan. Data analysis used repeated-measures ANOVAs with treatment and sex as between-subject factors and time as the within-subject factor.
Results: In controls, λ-Carrageenan reliably increased pain sensitivity to heat (hyperalgesia) and mechanical pressure (allodynia) and produced paw edema. Compared to vehicle, 3 mg/kg THC attenuated λ-Carrageenan-induced hyperalgesia and allodynia (both $p > 0.05$). THC alone at the 1 mg/kg dose, but not 3 mg/kg dose, increased paw edema compared with vehicle ($p > 0.05$). CBD alone did not alter λ-Carrageenan-induced increases in pain-sensitivity or inflammation ($p < 0.05$). Co-administration of 3 mg/kg THC + 10 mg/kg CBD decreased the anti-allodynia observed with 3 mg/kg THC alone. Co-administration of 3 mg/kg THC with 10 or 30 mg/kg CBD increased paw edema compared with 3 mg/kg THC alone (p's > 0.05).
Conclusions: These data demonstrate that a modest THC dose can reduce inflammatory pain, whereas CBD alone had no effect. CBD did not augment THC's effects and some doses of CBD diminished THC's analgesic effects. These findings suggest oral THC isolates are superior to using oral CBD isolates or THC+CBD products for inflammatory pain.
Financial Support: Supported by Departmental funds from Johns Hopkins University.

Acute Pain Sensitivity Varies as a Function of Weekly Delta-9-Tetrahydrocannabinol Exposure

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Drug Category: Cannabis/Cannabinoids
Topic: Other, Pain and Analgesia
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research
Aim: Pain is one of the most common indications for medical cannabis use. Acute cannabis and cannabinoid administration reduces pain response in healthy volunteers and some patient populations with reported sex differences. However, the extent to which frequent exposure to delta-9-tetrahydrocannabinol (THC), the main psychoactive constituent of cannabis, in the absence of acute administration, influences sensitivity to pain, and how this may differ between males and females, has not been systematically examined. In the present analysis, we investigated the association between self-reported weekly THC exposure, in healthy male and female participants who reported using cannabis ≥ monthly, and behavioral and subjective measures of acute pain using a Cold Pressor Test (CPT), an experimental pain test that has predictive validity for therapeutics used to treat chronic pain.
Methods: Weekly THC exposure was calculated using average cannabis use days per week in the past month multiplied by estimated daily THC consumption. After biochemical confirmation of cannabis abstinence for at least twelve hours, 57 healthy adults (21F, 36M; 30.7 +/- 7.6 years) who reported using cannabis an average of 4.7 +/- 2.3 days per week in the past month completed a CPT. During the CPT, participants immersed their hand in cold water (4°C) and time to report pain (pain threshold) and time to withdraw hand (pain tolerance) were recorded. Subjective pain ratings of the cold-water stimulus were measured using the Short-Form McGill Pain Questionnaire (SF-MPQ) and the 'Painfulness' and 'Bothersomeness' scale. Mixed effects models were used to predict the effects of weekly THC exposure, sex, and their potential interaction on all outcome measures (alpha = 0.05).
Results: Greater weekly THC exposure was associated with lower pain threshold ($F_{threshold} = 6.7$, $p > 0.001$) and tolerance ($F_{tolerance} = 6.4$, $p > 0.001$), as well as greater subjective ratings of pain (FSF-MPQ = 4.2, $p > 0.001$; FPainful = 10.6, $p > 0.001$, FBothersome = 5.9, $p > 0.001$). There was no significant effect of sex, or interaction between weekly THC exposure and sex, on any of the outcome measures.
Conclusions: Overall, greater THC exposure in healthy, recently abstinent individuals who use cannabis ≥ monthly was related to decreased pain threshold and tolerance, and increased subjective ratings of pain, and did not vary by sex. These findings suggest frequent THC exposure may impact sensitivity to painful stimuli, a factor that should be considered in the clinical use, and study of, cannabinoids as potential analgesic therapies.

Financial Support: US National Institute on Drug Abuse (R01DA047296), the Semel Charitable Foundation, and IRACDA at UCLA (K12GM106996).

Pain and Sociodemographic Correlates of Cannabis Use Among Patients With Insomnia in the 'All of Us' Research Program

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Drug Category: Cannabis/Cannabinoids
Topic: Epidemiology
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research
Aim: More than half of patients with insomnia report chronic pain, leading to potential self-medication with cannabis and addiction. Insomnia data from electronic health records (EHR) can add valuable information above self-report assessments. Accordingly, we analyzed EHR and self-report data from the NIH All of Us research program to investigate associations of past 3-month cannabis use with pain and socio-demographic factors.
Methods: The sample included 2000 individuals with insomnia, M (SD) age 58.2 (14.2), 63.8% female. Median pain intensity for cannabis users was 5 (IQR: 2-7), compared to 3 (IQR: 1-6) for non-users on a 10-point scale. We used Chi-square tests and logistic regression in R to examine associations of cannabis use with pain and sociodemographic factors.
Results: Thirty percent reported cannabis use in the past 3 months. Adjusted logistic regression indicated that a unit increase in pain intensity increased the odds of cannabis use by 6% (ORa = 1.06, CI [1.02; 1.11], p = 0.003). Black/African American and Latino participants were more likely than White participants to use cannabis (ORa = 2.24, CI [1.69; 2.96], p> 0.001 and ORa = 1.53, CI [1.03; 2.28], p> 0.05, respectively). Participants with $50,000–75,000 and< $75,000 income were less likely to use cannabis compared to participants with>$25,000 (ORa = .55, CI [0.38; 0.79], p> 0.01 and ORa = .63, CI [0.47; 0.86], p> 0.01, respectively). While age had a negative association, tobacco and alcohol use showed a positive association with cannabis use.
Conclusions: Thirty percent of insomnia patients used cannabis in the past 3 months, compared to 9% in the general population. Increased pain levels were associated with cannabis use, indicating potential self-medication for pain relief. More research is needed to develop efficacious and accessible treatments for pain and insomnia, especially among underrepresented groups.
Financial Support: LGL was supported by the UF Substance Abuse Training Center in Public Health from the National Institute of Drug Abuse (NIDA) of the National Institutes of Health under award number T32DA035167, CLQ was supported by the National Institute on Drug Abuse (NIDA) from the National Institutes of Health, grant K01DA046715. The content is solely the responsibility of the author(s) and does not necessarily represent the official views of the National Institutes of Health.

Effects of Repeatedly Administered Cannabis With THC and CBD on Experimental Pain and Abuse-Related Outcomes in Humans

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Drug Category: Cannabis/Cannabinoids
Topic: Tolerance/Dependence
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research
Aim: Though most medical cannabis patients cite pain relief as their primary indication, little is known about how (1) cannabis effects on pain and abuse liability change with daily administration and abrupt cessation,

and (2) the relative concentrations of tetrahydrocannabinol (THC) and cannabidiol (CBD) affect these outcomes. Herein we present preliminary human laboratory investigations addressing these questions.
Methods: Nontreatment-seeking daily cannabis users (N = 10) were enrolled in one of two 15-day inpatient conditions varying in type of cannabis administered (THC or CBD:THC). Each day, participants smoked cannabis cigarettes 3x/day, with strength varying across days: Day 1: active cannabis (THC condition: ~78 mg; CBD:THC condition: ~30mg CBD + ~18mg THC); Day 2-8: placebo cannabis; Day 9-15: active cannabis. We assessed the effects of repeated cannabis use and abstinence from active cannabis on cold pressor experimental pain and intoxication ('high'). Data collection is ongoing.
Results: In the THC condition, active cannabis administration following 7 days of abstinence (placebo cannabis) produced a 63% increase in analgesic effects and an 84% increase in ratings of 'high' relative to baseline (Day 1). Tolerance developed to both the analgesic and intoxicating effects following 7 days of active cannabis administration (Day 9 vs. Day 15). The CBD:THC condition produced minimal changes in pain response vs. placebo. However, following 7 days of abstinence, CBD:THC produced a 111% increase in ratings of intoxication relative to baseline; this effect did not change with repeated administration.
Conclusions: Understanding the impact of daily cannabis use and abrupt abstinence is a public health necessity. Our findings suggest that cannabis differing in THC:CBD produces distinct effects: 1) analgesic tolerance develops to high-THC cannabis; (2) tolerance develops to THC cannabis' abuse-related effects, and is reversible with abstinence. These patterns are not seen with CBD cannabis with lower THC content.
Financial Support: This study is supported by Alkermes and NIDA DA050752.

ORAL SESSION: INTERSECTING PERSPECTIVES ON SUICIDALITY AND SUBSTANCE USE

Trauma and Suicide Screening Outcomes Among Hospitalized Adults With Opioid Use Disorder and Serious Injection Related infections: Baseline Characteristics From an Ongoing Randomized Clinical Trial

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Drug Category: Opiates/Opioids
Topic: Comorbidities, Substance Use Disorder
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research
Aim: Persons with an opioid use disorder (OUD) have increased risk for medical hospitalization, trauma experiences, and prior suicide attempts. The aim is to describe the prevalence and types of traumatic experiences and suicide screening outcomes among persons with an OUD currently hospitalized with a serious injection-related infection (SIRI).
Methods: The Outpatient Parenteral Antimicrobial Therapy Plus Buprenorphine for OUD and SIRI study (NCT04677114) is a randomized, 2-arm clinical trial enrolling adults while hospitalized for SIRI. Participants are randomized 1:1 to either discharge once medically stable to an integrated buprenorphine and infectious disease outpatient care model or to treatment as usual. Preliminary baseline responses to the Brief Trauma Questionnaire (BTQ), Primary Care Posttraumatic Stress Disorder screen for DSM-5 (PC-PTSD-5), Mini International Neuropsychiatric Interview from the DSM-5 (MINI), and Columbia Suicide Severity Rating Scale (C-SSRS) are reported.
Results: The first 55 participants randomized are included herein. Trauma screening assessments showed 31 (56%) experienced ≥3 traumatic events. The two most common were having a life-threatening illness (n=41, 75%) and witnessing or fearing death/serious injury of another (n=40, 73%). Seventeen persons (31%) screened positive for probable PTSD and 5 (9%) met PTSD criteria per the MINI. The top three non-medical traumas mentioned in the description section of the PC-PTSD-5 were witnessing an overdose (n=32), being in a serious car accident (n=19) and experiencing gun violence (n=8). Of 8 (15%) participants who attempted suicide, 7 (88%) reported overdose as the method. Of 21 (38%) participants endorsing a wish to be dead, 8 (38%) had a passive death wish due to pain of having an OUD.

Conclusions: This patient sample is highly impacted by trauma and at risk for suicide. Greater understanding of the complexity of this population's life experiences, coupled with therapeutic approaches that emphasize strengths and integrated medical and OUD/psychiatric treatment, may improve health outcomes.
Financial Support: R01DA048892 (MPI Fanucchi/Lofwall)

Quantifying the Impact of Opioid Agonist Treatment on Suicide Mortality in New South Wales, Australia: A Population-Level Analysis from 2001 to 2020

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Drug Category: Opiates/Opioids
Topic: Epidemiology
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research
Aim: Few interventions have proven effective in reducing suicide at a population-level. Opioid agonist treatment (OAT) significantly reduces the substantial risk of suicide in individuals with opioid use disorder (OUD), however, its population-level impact is unclear. This study quantifies the impact of a large-scale OAT program on lowering suicide-related mortality among people with opioid use disorder (OUD).
Methods: We analysed a comprehensive linked dataset of 49,359 people who ever received OAT in New South Wales, Australia from 2000 to 2018. Using a dynamic mathematical model to simulate data from 2001 to 2020, we compared the number of suicide-related deaths under the current OAT program to a scenario without OAT. The model estimated the number of suicide-related deaths averted with 95% Credible Intervals (95% CrIs) for both scenarios in the prison and in the community and determined the overall percentage of suicides averted. Model validation was conducted by comparing the suicide-related deaths estimated by the model for the OAT scenario against the actual recorded suicides in the dataset from 2000 to 2017.
Results: We estimate that between 2001 and 2020, the provision of OAT in New South Wales averted 337 suicides (95% CrI: 213-492), with 325 (95% CrI: 202-476) in the community and 13 (95% CrI: 0-46) in prison, translating to 35% (95% CrI: 27%-43%) overall suicide reduction, and 27% (95% CrI: -2%-66%) in prison. Validation against real-world data up to 2017 supported the model's accuracy.
Conclusions: Our findings suggest that the OAT program in New South Wales has a substantial role in reducing suicide at the population-level. This emphasises the importance of OAT in reducing suicide risk among people with OUD and its critical importance as a public health intervention.
Financial Support: The funder had no influence over the study design, implementation or write up. The authors were supported by multiple funding sources including the National Institute on Drug Abuse (NIDA) (grants DP2DA049295, R01DA044170-03S1, R01DA1104470), the San Diego Center for AIDS Research (CFAR, AI036214), the Department of Veterans Affairs, the James B. Pendleton Charitable Trust, and the National Institute of Allergy and Infectious Diseases (NIAID; grant R01AI147490). The National Drug and Alcohol Research Centre, UNSW Sydney, is supported by funding from the Australian Government Department of Health under the Drug and Alcohol Program.

Repetitive Transcranial Magnetic Stimulation for the Treatment of Suicidality in Opioid Use Disorder: A Pilot Feasibility Randomized Controlled Trial

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Drug Category: Opiates/Opioids
Topic: Treatment
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research

Aim: Opioid use disorder (OUD) is a devastating condition where suicidality is common, contributing to overdose deaths. Repetitive transcranial magnetic stimulation (rTMS) to the dorsolateral prefrontal cortex (DLPFC) is used therapeutically in depression. We piloted a randomized, double-blind, sham-controlled trial of bilateral rTMS for patients with OUD and major depressive disorder experiencing suicidality.
Methods: Personalized targeting was conducted through individual Magnetic Resonance Imaging (MRI). We delivered a faster, more efficient form of rTMS called theta burst stimulation bilaterally to the DLPFC, once daily (total 20 treatments). Our primary objective was to determine feasibility of the protocol. The primary clinical outcome was the scale for suicidal ideation (SSI), with secondary outcomes including depression symptoms (Hamilton Rating Scale), and opioid cue-induced craving. ClinicalTrials.gov:NCT04785456.
Results: Eighty-seven individuals were pre-screened. Most common reasons for ineligibility including being lost to follow up, unable to commit to scheduling/travel requirements, and medical/psychiatric instability. Six participants (5:1 M:F) were enrolled, three randomized to each arm, four had a history of fentanyl use, two completed per protocol (1/arm). Participants received an average of 12 sessions; drop out was mostly due to missed sessions requiring withdrawal and not due to side effects. There were no serious adverse events. Of the participants with any follow data, SSI scores decreased numerically in 2/3 in the sham arm and 2/2 in the active arm; depression and opioid craving scores decreased in all.
Conclusions: We present the first data piloting an MRI-guided, outpatient, multi-session rTMS treatment course in patients with suicidality and OUD in the current North American context (an opioid overdose epidemic and rise of highly lethal synthetic opioids). We found low recruitment and retention rates given the highly unstable medical and psychosocial context of individuals struggling with this complex comorbidity. Future trials will require more practical, patient-oriented protocols to increase feasibility.
Financial Support: PSI Foundation

Monday, June 17, 2024

ORAL SESSION: DISCUSSING OPIOID WITHDRAWAL IN MONTREAL

Heightened Insula Signal but Reduced Interoceptive Awareness is Linked to Relapse in Opioid Use Disorder: Preliminary Findings

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Drug Category: Opiates/Opioids
Topic: Imaging
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research
Aim: Individuals with opioid use disorder (iOUD) experience gastrointestinal changes associated with aversive withdrawal symptoms (e.g., diarrhea, cramping). These changes, along with attenuated mid-insula brain signal to stomach sensations and reduced subjective awareness of bodily sensations, suggest that interoceptive processing is altered in iOUD when compared to healthy individuals. A crucial question, however, is whether these interoceptive metrics also predict iOUD relapse.
Methods: At a baseline visit, iOUD (N=46; 12F, 34M) completed the Visceral Interoceptive Attention (VIA) task during functional magnetic resonance imaging (fMRI) and the Multidimensional Assessment of Interoceptive Awareness (MAIA-2). Participants were then classified as Abstinent (n=20) or Relapsed (n=26) based on urine drug screens and self-reported substance use at monthly follow-up visits. Welch's t compared groups on: (1) fMRI data for the VIA stomach versus visual target contrast; (2) VIA self-reported intensity of stomach versus target sensations; and (3) MAIA-2 scores. Hedge's g is reported for effect size due to unequal group sizes.

Results: Compared to Abstinent iOUD, Relapsed iOUD: (1) exhibited greater left mid-insula signal (313 voxels) for the VIA stomach versus target contrast [t(39)=3.74, p=.0006, g=1.14]; and (2) reported lower MAIA-2 Total scores [t(36)=2.80, p=.008, g=0.86], driven by Body Trusting, Self-Regulation, and Attention Regulation subscales. However, groups did not differ on VIA intensity ratings [p=.59], and insula activation did not correlate with MAIA-2 Total in Relapsed iOUD [p=.32].
Conclusions: Relapse in iOUD is associated with increased neural activation to stomach sensations and difficulty trusting and regulating attention to bodily sensations. A framework for increasing relapse prediction accuracy based interoceptive processing during iOUD recovery is worth investigating.
Financial Support: R01DA050677 [PI: Stewart]

Scheduled, Short-Acting, Full Agonist Opioids for Opioid Withdrawal in the Hospital Reduces Rates of In-Hospital Illicit Opioid Use and Overdose

Payel Roy*[1]

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Drug Category: Opiates/Opioids
Topic: Treatment
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research
Aim: People with opioid use disorder frequently engage in in-hospital illicit substance use (IHSU) due to untreated pain and withdrawal and leave the hospital as patient-directed discharges. We developed a protocol to incorporate scheduled, short-acting, full agonist (SAFA) opioids into our practice with the goal of reducing rates of IHSU and overdose.
Methods: All patients seen by an inpatient addiction medicine consult service (AMCS) deemed at high risk of overdose from illicit opioids post-hospitalization were offered the intervention. We provided scheduled oxycodone and reassessed the patient to determine if dose escalation was required based on subjective report. We offered to initiate methadone or buprenorphine per patient preference through accelerated titration (methadone) and microinduction (buprenorphine). Once on a therapeutic dose of methadone or buprenorphine, we discontinued or tapered SAFA opioids. Outcomes included number of patients started on the intervention and number of episodes of IHSU and overdose, stratified by receipt of intervention at the time of IHSU.
Results: Eighty-two patients were started on scheduled short-acting, full agonist opioids for opioid withdrawal; 79 received oxycodone and 3 received hydromorphone. Typical starting dose of oxycodone was 20mg oral every four hours (total morphine milligram equivalence [MME] = 180) at the start of our intervention period; one year later, typical starting dose was 40mg every four hours (MME = 360) with a maximum of 70mg every four hours (MME = 630) offered to one patient. Six episodes of IHSU occurred among people who received SAFA opioids for opioid withdrawal; there were no overdoses. Thirteen episodes of IHSU occurred among people who were not initiated on the protocol, with three overdoses. No episodes of opioid overdose were related to initiation of SAFA opioids.
Conclusions: Aggressively managing opioid withdrawal with scheduled, SAFA opioids in the hospital is safe and has promise to reduce rates of in-hospital substance use and overdose.
Financial Support: None

NMDA Receptor Subunit 2B (GRIN2B) Genetic Variation Associated With Opioid Withdrawal Symptom Severity During Buprenorphine Induction

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Drug Category: Opiates/Opioids
Topic: Genetics/Proteomics/Metabolomics
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research

Aim: Animal research implicates the NMDA receptor 2B subunit (NR2B) in opioid dependence. Emerging clinical reports suggest NMDA receptor antagonism (ketamine) can attenuate buprenorphine-precipitated opioid withdrawal. This study examines whether NR2B gene (GRIN2B) variation, linked to risk of opioid use disorder, is associated with buprenorphine induction response.
Methods: Regular heroin users (n=44; 23 black/21 white), genotyped for GRIN2B variants, underwent fixed-dose buprenorphine induction (8 mg/day SL) for< 10 outpatient days before entering inpatient studies. Participants were instructed to remain opioid-abstinent< 8-hr prior to first buprenorphine dose. We measured opioid withdrawal and agonist symptoms prior to dosing each visit. Mixed-model ANCOVA (Genotype*(linear)Days [1-3]) and multiple regression analyses (day-1 scores) assessed effects of GRIN2B variation on withdrawal and agonist scores, controlling for current heroin use (M+SD=4.48+3.23 [$10-equivalent] bags/day).
Results: GRIN2B rs12829455 G/G homozygotes (n=19) reported higher M+SE withdrawal scores than A-allele carriers (n=21) primarily on day-1 (overnight abstinence, before initial buprenorphine dose), 29.6+3.5 vs. 15.8+3.6, compared to days 2-3, Genotype*Day p=.017, ηp2=.15, controlling for heroin use, Bags*Day p=.020, ηp2=.14. rs2300238 T/T homozygotes (n=6) reported non-significantly higher withdrawal than C-allele carriers (n=34) across days 1-3, Genotype p=.064, ηp2=.09. Other GRIN2B variants and self-reported race were not significant predictors. In regression analysis, current heroin use (B=.419, t=2.98, p=.005) and rs12829455 G/G vs. A-carrier genotype (B=.368, t=2.62, p=.013) predicted moderately-severe withdrawal scores on day-1, F(2,39)=7.11, p=.002, r2=.24. Current heroin use and GRIN2B genotypes did not predict agonist symptoms.
Conclusions: Controlling for current heroin use, GRIN2B rs12829455 G risk allele predicts clinically-elevated withdrawal symptoms prior to initial buprenorphine, but not thereafter, suggesting GRIN2B modulates pre-existing opioid physical dependence more than response to buprenorphine. Further research with larger samples should expand this analysis to higher-dose buprenorphine induction protocols, and examine whether NMDA receptor modulation (e.g. using ketamine, which partly acts through NR2B) could improve outcomes.
Financial Support: R01 DA015462; Gertrude Levin Endowed Chair in Addiction and Pain Biology; Michigan Dept. of Health and Human Services (Lycaki/Young Funds)

Lofexidine with Pregabalin for Managing Opioid Withdrawal: A New Use for an Old Drug?

Kyle Kampman*[1], George Woody[2], Sabrina Poole[1], Marc Fishman[3], John Mariani[4], Frances Levin[5], Kelly Spratt[1], Evgeny Krupitsky[6], Kevin Lynch[1]

[1]*University of Pennsylvania,* [2]*Perelman School of Medicine at the University of Pennsylvania,* [3]*Maryland Treatment Center,* [4]*Columbia University and New York Psychiatric Institute,* [5]*Columbia University Irving Medical Center/ New York State Psychiatric Institute,* [6]*V.M. Bekhterev National Medical Research Center for Psychiatry and Neurology*

Drug Category: Opiates/Opioids
Topic: Treatment
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research
Aim: Opioid withdrawal management using lofexidine or clonidine is often the first treatment for opioid addicted individuals who do not want or cannot access agonist maintenance. Though these medications suppress sympathetic overactivity, they have less effect on other opioid withdrawal symptoms and dropout is common. Observations and a randomized trial in Russia suggest that pregabalin reduces opioid withdrawal symptoms and treatment dropout. The aim of this trial was to test the combination of lofexidine and pregabalin for opioid withdrawal management.
Methods: Opioid-addicted individuals expressing interest in treatment with extended-release injectable naltrexone (XR-NTX) were admitted to inpatient treatment and randomized to decreasing doses of lofexidine and pregabalin or lofexidine and pregabalin placebo and offered XR-NTX on day 8. Ninety consenting participants were recruited across three sites, stratified according to gender, and randomized 2:1 to lofexidine + pregabalin or lofexidine + pregabalin placebo. Subjective and objective withdrawal was assessed twice/day; craving and suicidal ideation were assessed daily. Medications were withheld for excessive sedation or

postural hypotension. Non-opioid medications were used as needed for symptoms that study medication did not control. The primary outcome was the Short Opiate Withdrawal Scale-Gossup (SOWS). Secondary outcomes were completing withdrawal, receiving XR-NTX, and adverse events.
Results: The mean difference in SOWS scores over days 1-7 was 2.58 units (95% CI; 0.1-5.27) favoring pregabalin. Completion of withdrawal favored pregabalin (48% vs 30%, odds ratio of 2.07; 95% CI = 0.80, 5.39). Transition to XR-NTX was 20% in each group. There were no serious adverse events. Other adverse events were those typical of opioid withdrawal with no significant differences between groups.
Conclusions: The combination of lofexidine and pregabalin was safe, reduced opioid withdrawal symptoms, and increased the proportion of patients completing opioid withdrawal management compared to lofexidine alone.
Financial Support: NIDA grant 1 UG3 DA049694-01

ORAL SESSION: TAILS FROM THE LAB: ADVENTURES IN PRECLINICAL STIMULANT RESEARCH

Orexin Receptor Mechanisms Involved in Methamphetamine-Induced Sleep Disruption in Female Rhesus Monkeys

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Drug Category: Stimulants
Topic: Behavioral Pharmacology
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research
Aim: The aim of the present study was to investigate the extent to which orexin receptors mediate the effects of acute methamphetamine administration on actigraphy-based sleep parameters in female rhesus monkeys.
Methods: Actigraphy-based sleep measures was obtained in female rhesus monkeys (n=5) under baseline and acute test conditions, in which they received morning (10h) i.m. injections of saline or methamphetamine (0.3 mg/kg), and evening (17h30) oral treatments with vehicle, the non-selective orexin receptor antagonist suvorexant (1, 3, or 10 mg/kg, p.o.), or the OX2-selective orexin receptor antagonist MK-1064 (1, 3, or 10 mg/kg, p.o.).
Results: Similar to male monkeys, 0.3 mg/kg methamphetamine disrupted sleep in female rhesus monkeys. Treatment with either suvorexant or MK-1064 dose-dependently improved methamphetamine-induced sleep measures.
Conclusions: These findings suggest that orexin-mediated mechanisms play a role in methamphetamine-induced sleep impairment in female monkeys. Targeting the orexin system, in particular OX2 receptors, could be an effective option for treating methamphetamine-induced sleep disruptions observed in individuals with methamphetamine use disorder.
Financial Support: National Institutes of Health (DA011792, DA043204, DA046778, and DA049886)

The Effects of Amphetamine Treatment and Social Contact on the Reacquisition of Cocaine Self-Administration

Alexandra Johansen[1], Hannah Cha[1], Mackenzie Morris[1], Barry Yao[1], Samantha Biancorosso[1], Jacob Camp[1], Salome Hailu[1], Mark Smith*[1]

[1]*Davidson College*

Drug Category: Stimulants
Topic: Behavioral Pharmacology
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research

Aim: Relapse to cocaine use often occurs in a social context, and the presence of other individuals using cocaine may contribute to the likelihood of relapse. Previous studies have reported that chronic amphetamine treatment decreases relapse to cocaine use in humans and decreases reacquisition of cocaine self-administration in laboratory animals. The purpose of this study was to examine the effects of chronic amphetamine treatment on the reacquisition of cocaine use in laboratory rats self-administering cocaine in different social contexts.
Methods: Male and female rats were implanted with intravenous catheters and trained to self-administer cocaine on a fixed ratio (FR1) schedule of reinforcement in daily 6-hr sessions. After 14 days, cocaine self-administration was extinguished by substituting saline for the cocaine stimulus. At this time, rats were randomized to receive either chronic treatment with either amphetamine (3.0 mg/kg, sc, b.i.d.) or saline (1.0 ml/kg, sc, b.i.d.). After 9 days of extinction, cocaine was again made available on an FR1 schedule during daily 6-hr sessions. At this time, rats were further randomized into three social conditions: (1) rats self-administered cocaine in isolation, (2) rats self-administered cocaine in the presence of a same-sex partner that also self-administered cocaine, or (3) rats self-administered cocaine in the presence of a same-sex partner that did not have access to cocaine. Daily treatment with amphetamine or saline continued for the duration of reacquisition testing.
Results: Chronic treatment with amphetamine decreased responding during extinction and decreased cocaine intake during reacquisition. The presence of a social partner decreased the reacquisition of cocaine self-administration. Contrary to expectations, reacquisition of cocaine self-administration was lowest in rats that self-administered cocaine in the presence of a social partner that also self-administered cocaine. No sex differences were observed.
Conclusions: These data support previous studies demonstrating the efficacy of amphetamine to decrease cocaine intake and emphasize the importance of the social environment in relapse to cocaine use after a period of abstinence.
Financial Support: DA045364; DA031725

Modulatory Effects of Muscarinic M1 Receptor Agonist (VU0364572) in the Cellular Response to Cocaine in the Mice Nucleus Accumbens and Prefrontal Cortex

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Drug Category: Stimulants
Topic: Behavioral Pharmacology
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research
Aim: In the characterization of cocaine addiction, various of its rewarding and reinforcing properties have been studied. Recently, in-vivo fiber photometry (FP) monitoring of calcium in the nucleus accumbens (NAc) and prefrontal cortex (PFC) have provided relevant information in the understanding of acute cocaine effects. In addition, another interesting finding has been the potential effect of the M1 receptor-selective agonist VU0364572 on the cessation of cocaine-seeking behavior. Here, we hypothesized that VU0364572 has some potential neuromodulator properties over the in-vivo dynamics of calcium, in response to sub-chronic cocaine exposure (SCE), in the NAc and PFC of female and male mice.
Methods: Fiber photometry recordings were performed in C57Bl/6J mice between 8 to 10 weeks old, expressing the encoded virus biosensor pGP-AAV-syn-jGCaMP8m-WPRE. Animals were classified into six groups: Group A, male-NAc (n=5); Group B, male-PFC (n=5); Group C, female-NAc (n=5); Group D, female-PFC (n=5); Group E, male-NAc/PFC (n=3) and Group F, female-NAc/PFC(n=3), in the same hemisphere. Experimental plan: 1st experiment, Saline Exposure (SE), 15 min baseline recording plus 40 min recordings after saline. injection (one day). Next day 2nd experiment, SCE: same design but with cocaine injection (30mg/kg) for 5 days. After two weeks, 3rd experiment: testing VU0364572 (3.2 mg/kg), 30 min recording, Next day, experiment 4th: VU0364572 injection 30 min later cocaine injection. Finally, histological characterization of the brains examines virus expression and fiber tip location in the target areas.
>

Results: We have identified that cocaine reduced the number and amplitude of calcium peaks in the two brain regions, without showing sex differences. These responses were modulated by the pre-exposure to VU0364572 after 2 weeks of withdrawal.
>
Conclusions: These findings suggest that stimulation of the M1 receptor has the ability to regulate the response to cocaine in these two brain regions; Contributing to the understanding of the potential therapeutic mechanisms of this compound.
Financial Support: This research was supported by National Institutes of Health National Institute on Drug Abuse (NIH-NIDA) grant DA027825 (MT), Independent Research Fund Denmark grant 8020-00110B (MT).

The Effects of Male Versus Female Social Contact on Cocaine Self-Administration in Male Rats

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Drug Category: Stimulants
Topic: Behavioral Pharmacology
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research
Aim: Previous studies have reported that social contact reinforces cocaine self-administration. The purpose of this study was to examine whether the reinforcing effects of social contact on cocaine self-administration in male rats was influenced by the sex of a social partner.
Methods: Gonadally intact male rats were implanted with intravenous catheters and trained to self-administer cocaine on a fixed ratio schedule of reinforcement. The reinforcing effects of social contact on cocaine self-administration was examined on a progressive ratio schedule of reinforcement under conditions in which each response-contingent cocaine infusion resulted in 30-s access to either (1) a gonadally intact male rat, (2) an ovariectomized female rat, or (3) a black-and-white sock that was the same size and coloring of another rat (nonsocial control stimulus).
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Results: Social contact reinforced cocaine self-administration relative to the nonsocial control stimulus, but no differences were observed between the reinforcing effects of a male versus female social stimulus.
>
Conclusions: These data support previous studies reporting the social contact reinforces cocaine self-administration in male rats and indicate that the reinforcing effects of social contact are independent of the sex of the social partner.
Financial Support: DA045364; DA031725

ORAL SESSION: LEAFING THROUGH CANNABIS PREDICTIONS

Identifying Distinct Cannabis Use Disorder Symptom Profiles among Past-Year Cannabis Users in the United States: A Latent Class Analysis

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Drug Category: Cannabis/Cannabinoids
Topic: Epidemiology
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research
Aim: To identify subtypes of cannabis use disorder (CUD) symptoms among past-year cannabis users, which could be obscured by current diagnostic approaches.
Methods: A sample of respondents (n=12,528) 12+ years of age reporting past year cannabis use was drawn from the 2021 National Survey on Drug Use and Health. Latent class analysis was applied to identify

heterogenous subgroups of past-year cannabis users, based on patterns of 11 DSM-5 CUD symptoms. The association of subgroups with demographic and clinical characteristics, including past-year treatment utilization, was explored.
>
Results: A 4-class model provided the best fit: No Symptoms (68.1% of the sample); Time and Craving (23.1%), reporting time spent using/getting/getting over cannabis effects ('time') and craving; Uncontrolled Use (5.8%), characterized by using more than intended, time, craving, and tolerance; and Severe (3.1%), with a moderate to high probability (GREATER THAN 0.54) of most symptoms, except hazardous use (probability=0.3). Nearly all individuals in the symptomatic classes met criteria for at least mild CUD (2+ symptoms) (Time and Craving, mild: 71.6%, moderate: 25.6%, severe: 0.2%; Uncontrolled Use, moderate: 54.1%, severe: 45.9%; Severe, moderate: 5.9%, severe: 94.1%). Past-year treatment for cannabis-related problems was uncommon in each class (LESS THAN 2.3%) except for Severe (8.5%). Several symptoms had similar probabilities within classes, but differed across classes (e.g., time, tolerance, and craving; role impairment and continued use; unable to cut down and withdrawal).
>
Conclusions: Four distinct classes were identified representing CUD symptom profiles that varied both quantitively and qualitatively and were generally aligned with DSM-5 severity. Treatment for cannabis-related problems was unlikely, even among those reporting nearly all symptoms, pointing to high unmet need for treatment. Further, patterns of probabilities for specific symptoms within and across classes points to symptom clustering, which merits further research. These results suggest a heterogeneity of CUD that can inform development of individualized treatment programs.
Financial Support: Indivior Inc.

Using in Vitro Signalling Profiles of Cannabis Products to Infer in Vivo Biological Responses.

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Drug Category: Cannabis/Cannabinoids
Topic: Molecular Pharmacology
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research
Aim: Canada's cannabis legalization regulates THC and CBD levels to mitigate health risks, yet overlooks the complexity of cannabis product composition. Our study examines this complexity characterizing biological responses of cannabis extracts at CB1 and CB2 receptors.
To classify cannabinoids into functional categories and use the classification to evaluate their potential for desirable and undesirable in vivo effects.

Methods: We analyzed 28 different cannabinoids including cannabis extracts, pure cannabinoids, mixtures thereof, synthetic cannabinoids and terpenes.
Concentration response curves for each product were obtained in ten signaling outputs (arrestin recruitment and G-protein activation) following activation of CB1R or CB2R (N≥6). Our proprietary software performed automatic normalization and curve fitting. Pharmacological parameters describing product signaling efficacy were then compared and clustered algorithmically.

Computed similarities for each drug pair, allowed to classify all cannabinoids according to CB1R/CB2R responses. These measures of similarity provide a basis for inferring product potential for inducing desired and undesired in vivo effects.

>
Results: Multiscale bootstrap resampling computed approximate unbiased p values for rejecting the existence of clusters. Clusters of cannabinoids with $p<0.01$ and displaying distinct responses at CB1R/CB2R are:

- Inverse agonists such as CBD, the 'non-psychoactive' component of cannabis.
- Non-efficacious products such as beta-caryophyllene a terpene found in strains of cannabis.
- Low to medium efficacy cannabinoids such as Extract-II containing a 1:1 THC:CBD ratio.

- Medium to highly efficacious agonists such as THC, the main psychoactive component in cannabis
- Full agonists, such as the synthetic cannabinoid Win-55,212-2.

Signaling similarity among cannabinoids correlated with CB2R-mediated analgesia ($r^2=0.93$, $p<0.01$).

>

Conclusions: Our approach treats cannabis extracts as singular entities, and compares their signalling profile to that of pure cannabinoids. This methodology provides a basis for inferring potential in vivo effects of cannabis products from their signalling profiles.

Financial Support: Supported by Canadian Institutes of Health Research and Fonds d'Accélération des Collaborations en Santé.

Identifying Subtypes of Cannabis Use Disorder and Cannabis Consumption Predictors among Daily Cannabis Consumers

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Drug Category: Cannabis/Cannabinoids
Topic: Substance Use Disorder
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research

Aim: With therapeutic and daily cannabis use increasingly common among U.S. adults, there is a pressing need to define and differentiate types of problematic use particularly among daily consumers. Patterns of endorsement of the 11 criteria that comprise the DSM-5 Cannabis Use Disorder (CUD) diagnosis offer one potential meaningful characterization of problems associated with cannabis misuse. This study used latent class analysis (LCA) to identify distinct classes of cannabis-related problems among daily consumers based on DSM-5 CUD criteria, and then explored the association between classes and various aspects of cannabis consumption.

Methods: Participants (n=4140) recruited through Facebook completed a personalized survey measuring cannabis behaviors: reasons for use, methods of administration, frequency, quantity, and product potency. DSM-5 CUD criteria were assessed with 16 items adapted from national surveys. LCA identified classes of individuals based on CUD criteria endorsement patterns. ANOVA and chi-square analyses were used to test associations between classes and cannabis behaviors.

>

Results: LCA of the CUD criteria endorsement resulted in a 5-class model: Common Problems (45%) comprised individuals with mild CUD (2-3 criteria; spending a great deal of time, craving); Minimal Problems (30%) comprised individuals that endorsed zero or only one criteria; Physical Dependence Problems (16%) comprised those with moderate to severe CUD (4+ criteria; tolerance, withdrawal); Social, Physical and Emotional Problems (6.6%) comprised those with mild to moderate CUD (2-4 criteria; continued use despite physical/emotional consequences, social problems); and Severe Problems (3.1%) comprised those with severe CUD (6+ criteria). Preliminary contrasts revealed differences ($p<.01$) among classes in reasons for use, methods of use (smoking, vaping/dabbing, edibles), frequency, and quantity.

>

Conclusions: Results support substantial heterogeneity in DSM-5 CUD criteria even among daily consumers, including a majority that had none to mild problems related to use. Data from this study can guide treatment targets specific to patterns of reported problems.

Financial Support: This work was supported by the National Institutes of Health [NIDA R01DA050032; P30DA029926; T32DA037202].

Endocannabinoid Serum Concentrations Among Cannabis-Using Adults: Does Sex Moderate Associations With Cannabis Use Characteristics?

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Drug Category: Cannabis/Cannabinoids
Topic: Neurobiology/Neuroscience
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research

Aim: Cannabis is one of the most used substances in the U.S., with 6.9% of adults (age 18+) reporting past-year cannabis use disorder (CUD). Previous research has posited the role of the endocannabinoid system (eCB) in recovery from CUD. Further, cannabis craving and withdrawal severity were both associated with eCB levels during acute withdrawal. Yet, minimal research has identified differences in eCB levels by cannabis use characteristics, and whether these associations are moderated by sex.
Methods: Participants (n=144, 67% male) recruited across three RCTs had blood samples collected at pre-treatment sessions. eCB concentrations were quantified resulting in 2-aclyglycerol (2-AG) and anandamide (AEA) serum levels. Cannabis use severity (e.g., past three-month use patterns, THC-COOH, DSM-5 CUD symptoms, withdrawal severity, craving, and use history) were collected. Generalized linear models analyzed associations between eCB levels and cannabis use severity variables while moderating for sex and controlling for age and BMI.
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Results: All participants had positive THC urinary toxicology. Both 2-AG and AEA correlated with BMI, while 2-AG correlated with age and differed by sex. Across models, cannabis severity variables did not predict 2-AG or AEA serum concentrations. Cannabis craving-by-sex interaction was significantly associated with AEA, such that craving had a positive association with AEA, specific to females (p=.04). Associations between cannabis variables and 2-AG were not moderated by sex.
>
Conclusions: In a sample of regular cannabis-using adults at the outset of a treatment trial, eCB levels were not significantly predicted by cannabis use characteristics. One sex-specific finding emerged for female participants, such that increased cannabis craving was associated with AEA levels, bolstering previous sex-specific investigations of eCB levels within cannabis-using adults. However, lack of findings may be due to several factors, including eCB levels measured prior to treatment (i.e., no specified abstinence period) rather than after prolonged abstinence.
Financial Support: F31DA054761 PI: Sullivan, R. M.; K23DA048132 PI: Crane, N. A.

ORAL SESSION: INVESTIGATING AND TACKLING THE HIV/AIDS AND DRUG USE SYNDEMIC

Community-Based HIV Self-Testing among Persons who Use Drugs Can Reach Ending the HIV Epidemic Goals

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Drug Category: Opiates/Opioids
Topic: Infectious Disease (e.g., HIV, HCV)
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research

Aim: We assessed the feasibility and acceptability of providing HIV self-testing to persons who use drugs and determined interest in HIV pre-exposure prophylaxis (PrEP).
Methods: Between April 2023-July 2023, 40 individuals (n=40) met inclusion criteria and were supplied with rapid saliva-based HIVST, OraQuick® with same-day results. We administered questionnaires collecting demographics, sexual and substance use history, satisfaction with using HIVST and interest in PrEP at two community-based harm reduction centers.
>

Results: Participants mean [SD], age 37 [9] years; 68% White, 18% Black, 18% Latino, 5% Indigenous, 5% other; 85% female, 5% male, 5% non-binary, 5% other. Over the past 6 months, 43% shared injection equipment, 68% injected substances and 77% received money or gifts as a favor for sex. Sixty-three percent reported condomless sex. Eight percent (3/40) had newly reactive HIV tests. Eighty percent knew about PrEP, and 82% were interested in receiving it. All who completed HIVST agreed the kits were easy to use and would recommend it.
>
Conclusions: Partnering with community-based organizations to expand HIVST was feasible and acceptable. HIVST also identified new HIV cases. It addresses the Diagnose and Response pillars of the US Ending the HIV Epidemic (EHE) program. The current approach helped in early diagnosis and response to HIV outbreaks. Future studies should focus on using HIVST to address the Prevent and Treat EHE pillars by increasing access to HIV prevention tools such as PrEP and expedited HIV treatment.
Financial Support: This work was supported by the National Institute of Health [NIDA K23DA044085, NIDA K23 DA044085-03S1, NIAID 5P30AI042853 to S.A.A] and a Boston University School of Medicine Department of Medicine Evans Career Investment and Evans Junior Faculty Merit Awards to SAA.

Differences in Methamphetamine Use and Self-Reported Impact by Gender and Sexual Orientation in a Multisite U.s. Cohort of People with Hiv in Care

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Drug Category: Stimulants
Topic: Sex/Gender Differences
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research
Aim: To identify differences in methamphetamine (MA) use patterns and impact by gender among women, and sexual orientation among men, in a multisite U.S. cohort of people with HIV (PWH) in care.
Methods: We queried 3-month drug use and perceived impact by drug type, using a modified version of the ASSIST self-administered in routine care. Women were grouped by gender (cis or trans) and cis-gender men by sexual orientation by behavior or identity. Differences in drug use and impact were assessed using chi-squared and t-tests. We also used linear and logistic regression models for each drug use measure and adjusted for age and race/ethnicity.
>
Results: Among PWH [n=14924, 77% cisgender men: 57% men who have sex with men (MSM), 15% men who have sex with women (MSW), 5% men who have sex with men/women (MSMW); of women, 21% cisgender (CW), 2% transgender (TW)], 31% reported ever using MA; 10% reported current use. By gender group, a greater proportion of TW reported current MA (15%) than other groups, followed by MSM (14%), MSMW (13%), MSW (6%), and CW (3%)($p<0.001$). TW and CW MA users were more likely to report daily/almost daily use compared to MSM (36%, 32%, respectively, vs. 22% among MSM, $p=0.03$,$p=0.04$). Among PWH currently using MA, CW, MSW, and MSMW more often also reported past 3-month cocaine/crack (28-30% vs. 18%) and illicit opioid use (21-35% vs. 11%)(all $p<0.05$). TW were more likely to report health, social, legal, or financial problems (70% vs. 43%)($p=0.001$). Mean ASSIST scores were significantly higher among TW (18.0 vs. 14.2 among MSM,$p=0.02$). Comparisons from linear and logistic regression models adjusted for race/ethnicity yielded similar significance results.
>
Conclusions: MA use, impact and ASSIST score differ by women's gender and cis-men's sexual orientation, demonstrating a need for further inquiry into moderating factors and tailored harm reduction interventions.

Financial Support: NIDA R01 DA058938, NIDA U24DA058307

Opioid-associated Dysregulation of CD14+ Monocytes Among People Living with HIV

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Drug Category: Opiates/Opioids
Topic: Infectious Disease (e.g., HIV, HCV), Innate Immunity
Abstract Detail: Preclinical - In Vitro
Abstract Category: Original Research

Aim: Changes in monocyte (innate immune cells) phenotype and function are linked to chronic disease in people-living-with-HIV (PWH). Opioid-use-disorder (OUD) among PWH is associated with changes in monocyte phenotype. Here we compared transcriptional and functional responses of monocytes, and systemic markers of monocyte activation, between PWH with and without OUD.
Methods: Peripheral blood mononuclear cells (PBMC) and plasma from 27 PWH/OUD+ (participants in Comparing Treatments for HIV positive opioid users in Integrated Cost Effectiveness study – II CTN-0067) and 47 PWH/OUD- participants was collected. Plasma was utilized for sCD163 and sCD14 ELISAs. Monocytes were isolated from PBMC (PWH/OUD+, n=5; PWH/OUD-, n=7) and stimulated with lipopolysaccharide (LPS) or rested for 18hr. Monocyte RNAseq and a 33-cytokine array were performed. Differentially expressed genes (DEGs; defined by false discovery rate (FDR)>0.05) were identified between monocytes isolated from PWH with and without OUD, and gene set enrichment analysis (GSEA) performed using Molecular Signatures Database.
>
Results: Resting monocytes from PWH/OUD+ ± HIV viremia had dysregulation of pathways driving inflammation and cellular metabolism: reactive oxygen species (FDR 0.003), glycolysis (FDR 0.015), and pentose phosphate pathway (FDR 0.015). Monocytes from PWH/OUD+ ± HIV viremia demonstrated reduced capacity to produce pro- and anti-inflammatory cytokines in response to LPS: IL-10, IL-1β, TNF-α ($p<0.001$; Mann-Whitney) and IFN-γ ($p=0.018$; Mann-Whitney) when compared to PWH/OUD-. PWH/OUD+ demonstrated elevated systemic sCD163 and sCD14 ($p=0.002$ and $p<0.001$, respectively; Mann-Whitney) when compared to PWH/OUD.
>
Conclusions: Monocytes from PWH/OUD+ have altered transcriptomic and functional responses at rest and following stimulation characterized by alterations in pathways supporting metabolism, and decreased capacity to produce both pro- and anti-inflammatory cytokines. PWH/OUD+ demonstrate elevation in sCD14 and sCD163, biomarkers reflecting monocyte activation and risk of morbidity and mortality among PWH. Our findings support that chronic opioid exposure drives innate immune dysregulation among PWH through alterations in monocyte immunometabolism.
Financial Support: NIH/NIDA: R01DA046229; 5UG1DA015815

The Landscape of HIV Services Delivery in U.S. Syringe Services Programs: A Qualitative Exploration of Current Models and Opportunities

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Drug Category: Opiates/Opioids
Topic: Infectious Disease (e.g., HIV, HCV)
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research

Aim: To explore how diverse syringe services programs (SSPs) deliver HIV services across the U.S., where a resurgence in transmission has disproportionately affected people who use drugs (PWUD).
Methods: From May–November 2023, we recruited a purposive sample of SSPs offering HIV testing to PWUD. Qualitative interviews and thematic analysis explored current models of delivering HIV services, including HIV testing and prevention and treatment referrals.
>
Results: Twenty-three SSPs across the U.S. (Northeast: n=6; South: n=7; Midwest: n=4; West: n=6) were interviewed. Seventeen (74%) were nonprofit organizations; six (26%) were operated by health departments. Nine (39%) provided onsite confirmatory HIV testing via blood draw. We identified four overarching HIV services delivery models: (1) "Test and Refer," in which SSP staff provide HIV testing and make subsequent referrals to external HIV prevention and treatment services; (2) "Co-Located Services," in which external organizations sharing space with SSPs provide HIV testing and subsequent referrals; (3) "One-Stop-Shop," in which SSP staff provide HIV testing and directly navigate participants to HIV prevention or treatment services provided within SSPs; and (4) "Handoff," in which SSP staff provide participants with information about and referrals to local HIV testing and other services offered externally. Which HIV services delivery models were implemented was influenced by multilevel factors, including resource constraints (e.g., funding, staffing, space); perceived "fit" of HIV services within organizations' missions; participants' immediate needs (e.g., accessing syringes or buprenorphine); and external contexts in which other public health concerns were prioritized (e.g., local Hepatitis C or overdose epidemics).
>
Conclusions: SSPs are critical access points for HIV services for PWUD, especially vulnerable individuals injecting opioids. Yet, there is significant variation in delivery models implementation. Efforts to attend to multilevel implementation considerations and in turn optimize HIV services delivered through SSPs could help address HIV resurgence among PWUD.
Financial Support: This work was supported by the National Institute on Drug Abuse (NIDA; grants R01DA056883 and T32DA023356).

ORAL SESSION: SCIENCE AND REGULATION: PARTNERS IN PROGRESS

Pharmaceutical Stimulant Diversion, 2002-2022: Data from a National Sample of Law Enforcement and Regulatory Agencies

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Drug Category: Stimulants
Topic: Epidemiology
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research
Aim: Pharmaceutical stimulant medications methylphenidate and amphetamines are controlled substances in the U.S. Research suggests ongoing non-medical use and diversion of stimulant medications, yet, systematic data describing diversion rates at the national level are not apparent.
Methods: Data were drawn from a quarterly survey of pharmaceutical diversion completed by national sample of law enforcement and regulatory agencies who engage in drug diversion investigations. Quarterly population-based rates of pharmaceutical stimulant diversion (per 100,000) were calculated for the period 2002-2022. Analyses also examined changes in diversion rates following the COVID-19 pandemic.
>
Results: There were 3,324 methylphenidate cases and 12,875 amphetamine cases reported across all 50 states during the study period. Diversion rates are characterized by an accelerating increase over time, for methylphenidate ($t = 5.91$, $p > .0001$, $R2 = 0.299$) and amphetamines ($t = 11.76$, $p > .0001$, $R2 = 0.628$). Beginning in 1Q2020, amphetamine diversion rates decreased by half, coinciding with the COVID-19 pandemic. Trendlines prior to 1Q2020 indicate a sharp increase in amphetamine diversion rates over time ($t = 16.89$, $p > .0001$, $R2 = 0.801$). Diversion rates post-1Q2020 similarly show a sharp increase over time ($t = 2.99$, $p = .0151$, $R2 = 0.499$), with an accelerated increase compared to the prior period.

>
Conclusions: Findings show long-term increases in population-based diversion rates of pharmaceutical stimulants. Diversion rates decreased during the COVID-19 pandemic, yet rates have started to increase and are on a trajectory to exceed pre-pandemic levels. Continued monitoring and surveillance of diversion and NMU are warranted.
Financial Support: Denver Health and Hospital Authority

Overview of the Division of Therapeutics and Medical Consequences (DTMC) Regulatory Affairs Program

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[1]*National Institute of Drug Abuse/NIH/DHHS*

Drug Category: Other, Multiple Drugs of Abuse
Topic: Other, Regulatory Affairs
Abstract Detail: Other
Abstract Category: Program Descriptions
Aim: An overview of the Regulatory Affairs Program and other activities of the Regulatory Affairs Branch (RAB), Division of Therapeutics and Medical Consequences (DTMC), National Institute on Drug Abuse (NIDA) is presented. The RAB oversees the Regulatory Affairs Program which offers regulatory consultation and support to academic and industry investigators developing drugs, biologics, devices, or digital therapeutics applications to treat Substance Use Disorders (SUDs). The main objective of this program is to advance scientific knowledge of novel therapies and help companies obtain approval/clearance for new pharmaceutical or medical device products and ensure that the approval/clearance is maintained. The goals and objectives of the RAB are all conducive to promote fruitful interactions between the division or extramural investigators and the Food and Drug Administration (FDA) to support advancing the development of therapies through effective and appropriate regulatory pathways. RAB's services and activities also include supporting the NIDA's Drug Supply Program through the maintenance of Drug Master Files of products used in clinical trials in accordance with FDA regulations and guidance allowing for the distribution of methamphetamine, cocaine, and cannabis products to investigators.

Conclusions: In summary, RAB's role extends to the entire drug development process to assure that working relations with authorities are beneficial to the division and its partners in drug development for treating addictions. For more information about the Regulatory Affairs Program and to contact RAB staff please visit the DTMC Regulatory Affairs Program webpage (https://nida.nih.gov/about-nida/organization/divisions/division-therapeutics-medical-consequences-dtmc/research-programs#RAAMD).
Financial Support: None

Design and Illicit Manufacture of Synthetic Drugs

Michael Van Linn[1], Christine Herdman[1], Liqun Wong[1], Christine Herdman*[2]

[1]*United States Department of Justice,* [2]*DEA*

Drug Category: Other, Novel Psychoactive Substances and Precursor Chemicals
Topic: Chemistry
Abstract Detail: Other
Abstract Category: Theoretical/Commentary
Aim: To provide awareness on synthetic drugs and precursor chemicals used in the illicit manufacture of synthetic drugs.

Conclusions: Illicit drug manufacturers continue to evade domestic and international regulations by introducing uncontrolled synthetic drugs to user populations and by designing new precursor chemicals to

synthesize controlled substances. Proactive regulatory schemes are needed to address the continued evolution of synthetic drugs and precursor chemicals in effort to reduce illicit supply.
Financial Support: Diversion Control Division, Drug Enforcement Administration

Clearing the Air about Schedule I Controlled Substances Research

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Drug Category: Other, Schedule I Substances
Topic: Policy
Abstract Detail: Other
Abstract Category: Program Descriptions
Aim: The U.S. Controlled Substances Act (CSA) requires researchers to obtain a registration from the Drug Enforcement Administration (DEA) in order to conduct scientific or medical research with controlled substances. Schedule I controlled (CI) substances (e.g., MDMA, THC, psilocybin, heroin, etc.) are those that have a high potential for abuse, no accepted medical use, and a lack of accepted safety for use under medical supervision. As such, there is a tremendous need to further investigate CI substances, from basic-science applications that are critical to increasing our understanding and aiding in our decision-making to clinical investigations of potential therapeutics that may benefit our communities. There ought to be no stigma associated with the pursuit of this valuable research. Likewise, there ought to be no misleading accusations that the CSA and DEA are barriers to this important research when, in fact, the regulatory scheme protects research, prevents diversion, and disrupts unsafe promotion of substances by traffickers.

Conclusions: We will explain the straightforward process through which one obtains a CI research registration and our role in the review process as scientific staff of DEA. We will also provide a summary of active research areas over time, highlighting hallucinogens, cannabis/THC, and fentanyl analogues, and other informative statistics about the CI research program.
Financial Support: None

ORAL SESSION: BOOZE ON THE BRAIN: NEUROBIOLOGY OF ALCOHOL

Region-Specific Alterations of Orexin-A Neuronal Densities in the Hypothalamus of Rhesus Monkeys With Chronic Alcohol use

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Drug Category: Alcohol
Topic: Neurobiology/Neuroscience
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research
Aim: The orexin system plays an integral role in reward signaling and sleep. Thus, it represents a promising therapeutic target for both substance abuse and sleep disturbances in people with an alcohol use disorder (AUD). Orexin neurons are located in the lateral hypothalamic area (LHA) and the dorsomedial hypothalamus (DMH) and differentially innervate reward signaling areas based on their location. Preclinical studies suggest exposure to drugs of abuse such as opioids activates orexin neurons. However, studies investigating the effects of alcohol are less clear (i.e., reports indicate both an increase or decrease in orexin signaling). Specifically, these studies did not compare the LHA with the DMH. Furthermore, there is a lack of evidence regarding the orexin system in the hypothalamus of humans and nonhuman primates with chronic alcohol use, limiting translatability of preclinical findings. Therefore, the objective of the present study was to evaluate orexin-A neurons in the LHA and DMH of rhesus monkeys with chronic alcohol use.

Methods: Serial sections (n=5/monkey) of frozen hypothalamus samples from adult, male rhesus monkeys with a history of chronic alcohol use (n=7) or no alcohol (n=5) were used. Open-access (i.e., 22 hours/day) self-administration sessions occurred daily for 12 months, with average ethanol intake ranging between 2.55 and 3.78 g/kg/day. Sections were labeled with immunohistochemistry for orexin-A and counterstained with methyl green to identify hypothalamic cytoarchitecture. Neurons expressing orexin-A in hypothalamic subregions were quantified with stereology-based computer assisted light microscopy. Numerical densities of orexin-A neurons in the LHA and DMH were compared between groups using analysis of variance.
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Results: Our results identified significantly greater densities of orexin-A neurons in the DMH region ($p<0.03$) in monkeys with chronic alcohol use compared to monkeys without alcohol use. In contrast, densities of orexin-A neurons were significantly decreased in the LHA region of monkeys with chronic alcohol use ($p<0.05$).
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Conclusions: The current results suggest that orexin-A alterations are region-specific, potentially explaining discrepancies in prior studies. Furthermore, orexin-A alterations may impact alcohol use, contributing to the degenerative feedback cycle between sleep and alcohol consumption. Therefore, these region-specific changes may help identify orexin-based therapeutic strategies for AUD.
Financial Support: Supported by MH125833 (to HP) 1P20GM144041 (to BG) AA029023 (to DMP) and AA019431 (to KAG)

Epigenetics and Alcohol: The Histone Methyltransferase G9A Acts in Dynorphin-Positive Accumbal Neurons to Reduce Stress-Induced Potentiation of Ethanol Drinking in Mice

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Drug Category: Alcohol
Topic: Neurobiology/Neuroscience
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research
Aim: Stress perpetuates the cycle of excessive alcohol drinking and contributes to the transition to an alcohol-use disorder (AUD). A common mechanism that regulates both stress-sensitivity and alcohol use is epigenetic regulation of gene transcription. One epigenetic modifier implicated in models of AUD is G9a, a histone methyltransferase that dimethylates lysine 9 on histone 3 (H3K9me2). We recently showed that alcohol decreases G9a in the nucleus accumbens (NAc). Mimicking this reduction of NAc G9a with an AAV-mediated shRNA knockdown decreased stress-potentiated alcohol drinking; however, the mechanism is not fully understood. Here we investigated if there is a cell-type specific effect of NAc G9a. Since the dynorphin (Dyn) system plays a prominent role in stress/ethanol-related behaviors and dynorphin is present in a major subset of NAc neurons (NAcDyn+), we hypothesized that G9a acts selectively through (NAcDyn+) neurons - but not enkephalin-containing (NAcEnk+) neurons - to alter stress-potentiated drinking.
Methods: We injected a novel cre-dependent AAV virus (AAV-DIO-shG9a) into the NAc of both dynorphin-cre and enkephalin-cre mice. These mice underwent 4 weeks of two-bottle choice drinking (baseline) and then were injected with the kappa opioid receptor agonist U50,488 (5mg/kg, i.p.) before drinking.
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Results: Control Dyn-cre mice exhibited stress-potentiated drinking, but the G9a knockdown experimental mice did not, thus demonstrating an effect of G9a in NAcDyn+ neurons. In contrast, experimental Enk-cre mice did exhibit stress-potentiated drinking, suggesting no effect of G9a in NAcEnk+.
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Conclusions: Reducing G9a specifically in NAcDyn+ neurons reduces potentiated alcohol drinking in mice. Thus, G9a in NAcDyn+ neurons is required for stress-potentiated alcohol drinking. Targeting G9a or NAcDyn+ neurons could potentially help reduce escalated alcohol drinking in patients with AUD.
Financial Support: K01 DA046513

Investigating Sex-Specific Effects of Transcranial Magnetic Stimulation Targets on Alcohol Cue Reactivity

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Drug Category: Alcohol
Topic: Sex/Gender Differences
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research

Aim: Over the past decade, there has been an alarming rise in alcohol use disorder (AUD) among females. Considerable efforts have been directed toward investigating transcranial magnetic stimulation (TMS) as a therapeutic option for AUD. Two promising strategies include 10Hz to the dorsolateral prefrontal cortex (DLPFC) and intermittent theta burst stimulation (iTBS) to the medial PFC (MPFC). The aim of this study was to evaluate the relative efficacy of two potential TMS targets, the DLPFC and MPFC, as tools to decrease functional connectivity to alcohol cues in participants with AUD. Here, we investigated the difference in effects between males and females.

Methods: Sixty-eight individuals with AUD (57M/11F) completed three TMS sessions on separate days: 1) 10Hz DLPFC, 2) iTBS MPFC and 3) sham stimulation. Following each session, brain reactivity to alcohol cues was measured using fMRI. To evaluate functional connectivity, images were analyzed in the CONN toolbox. Fisher's transformed correlation coefficients were extracted between the MPFC and the following AAL atlas ROIs: insula, caudate, putamen, pallidum, anterior cingulate cortex, amygdala, superior occipital cortex. Functional connectivity during alcohol cue blocks was compiled for each participant at each visit. A general linear model was used to determine the relationship between sex and stimulation site on change in functional connectivity.

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Results: There was a significant sex by site interaction ($F_{1,83} = 13.365$, $p<0.001$). In females, MPFC stimulation produced a larger decrease in functional connectivity to alcohol cues while the DLPFC protocol suggests more significant reductions in males.

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Conclusions: While limited by a small sample of females, these results suggest that males and females with AUD may benefit from different TMS target sites. While TMS may be a promising intervention for AUD, understanding sex differences in AUD is imperative as we work toward establishing effective treatment strategies for both males and females.

Financial Support: Supported by T32 AA007565 and P50 AA010761.

Markers of Monocyte Activation and Inflammation and Mortality in Patients with Severe Alcohol Use Disorder.

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Drug Category: Alcohol
Topic: Epidemiology
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research

Aim: Patients with severe Alcohol Use Disorder (AUD) have a high mid-term mortality. There is a need for detecting potential predictors of death.

We aimed to analyze the association between markers of monocyte activation (sCD163 and sCD14) and of inflammation (Interlequin 6 [IL-6] and IL-10) and mortality in a cohort of patients with severe AUD admitted for hospital treatment of the disorder.

Methods: Longitudinal study in a cohort of patients admitted for treatment of severe AUD at Hospital Universitari Germans Trias i Pujol in Badalona and Hospital de Bellvitge in L'Hospitalet de Llobregat between June 2013 and october 2022.
To detect the association between markers of monocyte activation and inflammation in the highest quartile and mortality we performed Cox regression analyses adjusted by age and sex.

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Results: We included 463 patients (23% women) with a median age of 49.5 years (interquartile range [IQR]: 43-56). The median of alcohol intake before admission was 150 grams per day (IQR: 100-225) and the median duration of AUD was 20 years (IQR: 10-28). The median levels of sCD163, sCD14, IL-6 and IL-10 were 732 ng/ mL (IQR: 460-1000), 1.73 x 106 (IQR: 1.36-2.24), 3.28 pg/ mL (IQR: 1.07-7.76) and 0.56 pg/ mL (RIC: 0.02-2.01), respectively.
As of April 2023, 60 patients (13% of the total cohort) had died. The median follow-up was 3.8 years (RIC: 2.89-4.96) and the mortality rate was 3.1 per 100 patient-years. Patients with levels of sCD163, sCD14 and IL-6 in the highest quartile had a greater risk of death [hazard ratios of 2.92 (95% Confidence Interval [CI]: 1.96-5.04), 1.96 (95% CI: 1.14-3.36) and 2.33 (95% CI: 1.37-3.97), respectively].

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Conclusions: In this cohort of patients with severe AUD mortality was high. Patients with levels of sCD163, sCD14 and IL-6 in the highest quartile had a higher risk of death.
Financial Support: This research was partially funded by the Ministry of Economy and Competitiveness, Institute of Health Carlos III (RETICS RD16/0017/0003, Programa Juan Rodes JR20/00016, Programa Sara Borrell CD19/00019, grant PI20/00883, and Redes de Investigación Cooperativa Orientadas a Resultados en Salud (RICORS)-Red de Investigación en Atención Primaria de Adicciones (RIAPAd), grant numbers RD21/0009/0004), European Fund for Regional Development (FEDER), Ministry of Health, Social Services and Equality, National Plan on Drugs, Spain (grant 2020/024), Consolidated Research Group (2021-SGR-00945), Autonomous Government of Catalonia, Spain.

ORAL SESSION: DRUG USE INVOLVEMENT: INSIGHTS FROM THE ADOLESCENTS BRAIN COGNITIVE DEVELOPMENT STUDY

Impact of Pre-Adolescent Substance Familiarity on Subsequent use: Longitudinal Analysis of Risk by Latent Classes of Familiarity in the ABCD Sample

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Drug Category: Polydrug (i.e. concurrent use two or more drugs)
Topic: Prevention
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research
Aim: Predicting substance use in early adolescence is a difficult yet important task in developing effective prevention. We aim to extend previous findings on the linear associations between familiarity with (knowledge of) substances in middle childhood and subsequent use of any substance in early adolescence through the use of a latent class analysis (LCA) to create risk profiles based on substance familiarity.
Methods: Using the Adolescent Brain Cognitive Development (ABCD) Study®, we conducted an LCA using 18 binary substance familiarity variables (n=11,694 substance-naïve youth). Complementary analyses investigated the relationship between LCA groups and 1) longitudinal use, 2) use initiation, and 3) early use (> 14-years). Demographics and previously identified risk factors for adolescent use were included as covariates.

>

Results: The optimal LCA resulted in a four-class solution. These groups (Naïve, Common, Uncommon, and Rare) increased in both the number and rarity of known substances. The Common group was set as our reference level. There were no differences in use between the Naïve and Common groups across analyses. Analysis 1 revealed an increased risk in use over time among both the Uncommon and Rare groups (ORs=2.08

and 5.55, respectively, p's > 0.001) compared to the Common group. Similarly, Analysis 2 observed an increased risk in use initiation between the Uncommon and Rare groups and the Common group (ORs=2.08 and 3.42, respectively, p's<0.001). Analysis 3 found an increased risk in early use between the Common and Uncommon groups (OR=1.92, p > 0.001) with a similar trend between the Common and Rare groups (OR=1.90, p=0.06).
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Conclusions: Taken together, our results highlight distinct risk profiles for adolescent use based on substance familiarity in middle childhood. The current work may suggest a potential direction for developing an early screening tool for clinicians to identify those at risk for adolescent use.
Financial Support: Supported by NIAAA-F31-AA031435 and NIDA-U01-DA051016.

Investigating the Relationship Between Physical Activity and Substance Use Initiation and Experimentation in Adolescents From the ABCD® Study Cohort

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Drug Category: Other, Substance Use Initiation and Experimentation
Topic: Prevention
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research
Aim: Physical activity (PA) plays an important role in healthy brain development (e.g., through increasing BDNF, LTP, and neurogenesis). Adolescence is a period characterized by more risky behaviors, like using substances, can be detrimental to brain development. This study aims to determine if PA influences initiation and experimentation with substance use among adolescents. We predict that higher levels of PA will be associated with less substance use initiation and experimentation, and more vigorous PA having a larger effect compared to light PA.
Methods: A sample of 4,731 participants (Mage= 13.68; white: 69%; female: 47.9%) from the ABCD Study provided data on Fitbit-measured `minutes per day` of total PA, light PA, fair PA, and vigorous PA at the 2-year follow-up, and substance use outcomes at the 4-year follow-up. Substance use outcomes of experimentation (had a sip/puff/try of alcohol, tobacco, or marijuana) and initiation (had more than a sip/puff/try of alcohol, tobacco or marijuana, or anything else) were examined dichotomously. Logistic regression analyses were conducted, controlling for demographic factors and CBCL depression scores.
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Results: Increased total minutes of light PA was associated with a lower likelihood of experimentation (Estimate: -0.0003570, p = 0.007). More total minutes of fair PA increased the likelihood of initiation (Estimate: 0.002122, p = 0.014). Higher total minutes of vigorous PA increased the likelihood of initiation (Estimate: 0.004532, p> 0.0001) and experimentation (Estimate: 0.002602, p = 0.002). No significant associations were found for total PA and light PA with initiation, or fair PA with experimentation.
>
Conclusions: Results demonstrate a nuanced relationship between physical activity and substance use. Although increased light activity appears protective against experimentation, moderate and vigorous activities show an opposing association with initiation. Findings are consistent with prior work in adult samples linking exercise to substance use. Future research should examine underlying mechanisms or contextual factors accounting for these results.
Financial Support: U01DA041048, U01DA050989, U01DA051016, U01DA041022, U01DA051018, U01DA051037, U01DA050987, U01DA041174, U01DA041106, U01DA041117, U01DA041028, U01DA041134, U01DA050988, U01DA051039, U01DA041156, U01DA041025, U01DA041120, U01DA051038, U01DA041148, U01DA041093, U01DA041089, U24DA041123, U24DA041147.

Associations Between Behavioral and Self-Reported Impulsivity, Brain Structure, and Genetic Influences in Middle Childhood

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Drug Category: Other, none
Topic: Neurobiology/Neuroscience
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research
Aim: Impulsivity, or the tendency to act without forethought, undergoes a characteristic developmental trajectory from childhood to adolescence and into adulthood. Few large-scale studies have assessed associations between impulsivity, brain structure, and genetic predictors in children.
Methods: We analyzed children, ages 9-10, from the ABCD study (n = 9112), and explored relationships among impulsivity, assessed through the Urgency, Premeditation, Perseverance, Sensation Seeking Impulsive Behavior Scale (UPPS-P) self-report scale, delay discounting, brain structure (cortical thickness (CT), cortical volume (CV), and cortical area (CA)), and genetic polygenic scores for externalizing behavior (PGSEXT).
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Results: Higher UPPS-P total scores were associated with smaller CA in the left cuneus, middle temporal, and insula regions; right bankssts (banks of superior temporal sulcus), caudal middle frontal, and frontal pole regions; and in both left and right post central, precentral, rostral middle frontal, superior frontal, and superior temporal regions. Higher delay discounting (indicative of more impulsivity) was associated with smaller CA in left rostral middle frontal region; left and right middle temporal regions and left and right superior temporal regions. No associations were seen with CV or CT. PGSEXT was significantly associated with UPPS-P scores but not with delay discounting. PGSEXT was associated with smaller CA in right lateral orbitofrontal and paracentral regions, and with smaller CV in left rostral anterior cingulate, right inferior temporal, lateral orbitofrontal, and paracentral regions.
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Conclusions: These findings indicate that CA is a robust predictor of impulsivity, particularly measured by UPPS-P and is associated with genetic polygenic scores. Future work should assess these associations through adolescence, and study associated functional outcomes, such as substance use or psychopathology.
Financial Support: K02DA052684-01A1

Peer Victimization Mediates Age of First Exposure to Nicotine, Marijuana and Alcohol in Sexual Minority Adolescents in the ABCD Study

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Drug Category: Other, alcohol, cannabis, and nicotine
Topic: Disparities
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research
Aim: Lesbian, Gay and Bisexual (LGB) youth have earlier and higher rates of substance use than heterosexual peers. The minority stress framework suggests this disparity, and others, may be partially explained by the social stigma experienced by LGB individuals. We hypothesized that earlier exposure to substances by LGB adolescents compared to peers is moderated by LGB-specific discrimination and mediated by peer victimization.
Methods: Data release 5.0 from the Adolescent Brain Cognitive Development Study includes 11,868 adolescents, enrolled in 2015 at 21 sites across the United States at ages 9/10 years (48% assigned female). Time from study enrollment to visit reporting first puff of nicotine, puff of marijuana, full alcoholic drink or last attended study visit (censure; at most 4-year follow-up) was modeled using multilevel mixed-effects parametric survival analysis (exponential partial hazards) controlling for assigned sex, pubertal stage, age at enrollment (months), household income and nesting subjects within families to account for siblings. LGB

youth (22%) were categorized as ever reporting a lesbian, gay, bisexual, other or questioning sexual orientation. Peer experiences of relational, reputational and overt aggression were averaged across study visits. Ever experiencing LGB-specific discrimination was dichotomized.
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Results: After controlling for covariates, LGB youth were 2.3, 2.5, and 2.8 times more likely (p<.001) to have tried nicotine, marijuana, and a full alcoholic beverage, respectively, compared to heterosexual peers during their first 4 years in the ABCD study (by age 14). After including peer aggression and LGB-specific discrimination, the HRs dropped to 1.5 (p=.001) for nicotine, 1.7 (p=.002) for marijuana, and 1.9 (p<.001) for alcohol.
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Conclusions: Our findings are consistent with the minority stress framework, suggesting that aggression and discrimination experienced by LGB youth may contribute to the disparity in age of exposure to substances including tobacco, marijuana, and alcohol.
Financial Support: The ABCD Study is supported by the National Institutes of Health and additional US federal partners including the Centers for Disease Control and Prevention under award numbers U01DA041048, U01DA050989, U01DA051016, U01DA041022, U01DA051018, U01DA051037, U01DA050987, U01DA041174, U01DA041106, U01DA041117, U01DA041028, U01DA041134, U01DA050988, U01DA051039, U01DA041156, U01DA041025, U01DA041120, U01DA051038, U01DA041148, U01DA041093, U01DA041089, U24DA041123, U24DA041147. This study was supported in part by grant K08HL159350 from the National Institutes of Health (NIH).

ORAL SESSION: MORE THAN A SODA FOUNTAIN: PHARMACY IN HARM REDUCTION

A Multisite Implementation-Efficacy Trial of Pharmacist-Led Collaborative Care for Medication Assisted Treatment for Opioid Dependence: 3-Month Outcomes from the EPIC-MATOD Trial

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Drug Category: Opiates/Opioids
Topic: Treatment
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research
Aim: Prescriber shortages have led to limited access to Medication Assisted Treatment for Opioid Dependence (MATOD) in some parts of Australia. Collaborative care arrangements between pharmacists and prescribers are one means of increasing access to treatment.
The Enhancing Pharmacists Involvement in Care (EPIC)-MATOD study aims to evaluate the clinical and implementation outcomes of collaborative pharmacist-prescriber model of opioid agonist treatment. We hypothesised that pharmacist-led collaborative care would provide comparable outcomes to traditional treatment.

Methods: The study protocol was published prospectively; trial registration: ACTRN12621000871842. Participants (taking part in collaborative care, and a comparison group) were recruited into a multisite, implementation trial in Victoria, Australia. The model of care involves pharmacists conducting clinical reviews, dose adjustment and other tasks in addition to dosing. Participants are followed for 6-months with outcomes mapped to the RE-AIM framework. The primary clinical endpoint is treatment retention at 26 weeks. Secondary endpoints include substance use, mental and physical health, implementation costs, feasibility and acceptability.
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Results: Recruitment was completed in September 2023 (n = 85). The mean age of the sample was 44.9 yrs (SD 9.9), with 61.2% of the sample being male. Most (74.1%) participants are receiving methadone, with 23.6% on buprenorphine formulations (sublingual or injectable). There were no significant differences in treatment retention or substance use between the groups at 3-months. Participants in collaborative care

reported significant increases in treatment satisfaction at 3-months (t(49)=2.093, p=0.042), which was not observed in the comparison arm. Qualitative data from participants, pharmacists and prescribers indicate high support and acceptability of the model of care.
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Conclusions: Preliminary outcomes demonstrate acceptability and feasibility, with comparable clinical outcomes and greater treatment satisfaction for patients who are receiving opioid agonist treatment through collaborative care in community pharmacies. Pharmacist-led collaborative care may be an important innovation to increase access to opioid agonist treatment.
Financial Support: The study is supported by the Victorian Government through an Alcohol and Drug Research Innovation Agenda (ADRIA) Research Grant. SN is the recipient of an NHMRC Research Fellowship (#1169361).

Pharmacist Involvement in Motivational Interviewing Intervention for Patients with Prescription Opioid Misuse Behaviors

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Drug Category: Opiates/Opioids
Topic: Prevention
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research
Aim: Community pharmacists are an underutilized resource to address opioid medication misuse among patients. It is unknown in the field if high fidelity motivational interviewing (MI) targeting opioid medication misuse can be successfully integrated into structured medication therapy management (MTM) sessions delivered by pharmacists.
Methods: Design/participants: We conducted an exploratory analysis of recordings from three pharmacists who participated in one 16-hour MI training followed by monthly one-hour supervision sessions during 2 years of a behavioral health randomized clinical trial using MTM to target opioid medication misuse.
Procedure: 20-minute segments of sessions (N=47) that employed MI skills were coded using the MI Treatment Integrity Coding Manual (MITICM) 4.2.1.

Assessments/analyses: Frequencies/percentages and means were used to describe (1) demographic/health characteristics of intervention recipients and (2) fidelity of MI skills demonstrated by pharmacists including: global scores, complex/simple reflections, and MI adherent/non-adherent behavior counts. Competency is achieved with scores of 3 out of 5 in technical and 3.5 out of 5 in relational global scales and 40% rates of complex reflections. Proficiency-mastery is achieved with 4 out of 5 in technical and relational global scales and 50% complex reflections.

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Results: All intervention recipients reported opioid medication misuse, were approximately 50 years old, and were mostly White (78.7%). Recipients screened positive for ≥moderate severity: post-traumatic stress (59.6%), depression (51.1%), and opioid use disorder (29.8%). Relational and technical global scores averaged 3.6 and 3.8, respectively. Percentage of complex reflections averaged 60.2%. MI adherent behavior counts, on average, were 11 times greater than non-adherent behavior counts (adherent mean= 4.4, non-adherent mean=0.4) for all sessions.
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Conclusions: Pharmacists delivering MTM sessions targeting opioid medication misuse can effectively integrate MI skills and receive consistently competent and/or proficient scores following structured training/supervision. Pharmacists utilizing MI within MTM sessions have the potential to reduce misuse and opioid related risk.
Financial Support: NIDA R01DA051546

Secret Shopping to Assess Real-World Access to Over-The-Counter Naloxone in Community Pharmacies

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

Aim: Community pharmacies support harm reduction through dispensing the overdose antidote naloxone but access barriers persist. It is unclear whether new over-the-counter (OTC) naloxone products will reduce or exacerbate these challenges. As part of a four-state randomized trial designed to increase naloxone provision in two retail pharmacy chains through a multi-component educational and academic detailing intervention, we used secret shopping for protocol fidelity evaluation. The aim of the present study was to adapt and apply secret shopping in community pharmacies to identify facilitators and barriers to OTC naloxone access.
Methods: We revised study measures and trained 10 personnel to conduct in-person checks documenting OTC naloxone availability (following September 2023 product launch), placement, signage, medication communications, and purchase experience in a sample of study pharmacies.
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Results: From October to November 2023, 50 of 176 study pharmacies were assessed across Massachusetts (n=18), New Hampshire (n=19), Washington (n=9), and Oregon (n=4), representing both chains (n=37 stand-alone retail pharmacy, n=13 supermarket pharmacy). Of the 68% (n=34) that stocked OTC naloxone, none were supermarket pharmacies or in Oregon or Washington, though all pharmacies continued to provide prescription-only naloxone. 34% of pharmacies had signage about OTC naloxone or overdose prevention and, when stocked, OTC naloxone could be requested verbally or using a display card at the pharmacy counter or front registers. When available in-aisle, OTC naloxone was locked in a container until purchase (n=4) and inconsistently shelved alongside first aid, drug testing, or home monitoring products. Most pharmacy support staff lacked knowledge about naloxone in general as well as OTC availability.
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Conclusions: The onus of locating, learning about, and obtaining OTC naloxone in pharmacies is on the consumer but could be improved by clearer communications, consistent stocking and product placement, and targeted staff training. Adapting secret shopping for OTC fidelity provided critical insights into persistent and new naloxone access barriers.
Financial Support: NIDA R01DA045745

Development of the Brief Stigma and Perceptions Questionnaire for Pharmacists: A Confirmatory Factor Analysis Approach in New York State Counties Enrolled in the Healing Communities Study

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Drug Category: Opiates/Opioids
Topic: Behavioral Pharmacology
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research
Aim: Little is known about Pharmacists' attitudes as a possible barrier to linkage to Narcan and Medication for opioid use disorder (MOUD). We examine the psychometrics of a 65-item Pharmacist Opioid Use Disorder Perceptions Questionnaire, (P-OUDP-Q), a multi-dimensional measure designed to measure Pharmacists perceptions and perceived stigma towards Narcan, MOUD, pharmacy protocols, policies, access and distribution for high impact overdose communities. The study was conducted as part of the HEALing Communities Study in New York State (NYS).
Methods: A sample of 324 Pharmacists recruited from 16 counties in NYS between January-June 2022. We asked pharmacists about their level of familiarity with opioid-related medications, protocols, policies; attitudes regarding pharmacists' roles, confidence and beliefs centered around delivery of MOUD and Narcan. The questionnaire includes 31 questions. We conducted factor analysis to assess individual and community level factors associated with underlying constructs that were categorized. Factor scores were compared across the demographic predictors (race/ethnicity, gender, education, pharmacy type, location). Variables factor loadings less than 0.4 were eliminated from the factor analysis and the process was reiterated.
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Results: Most 86% (n=280) Pharmacists were white. The majority 57% were female (n= 186), 35% (n=113) were between 30-35 years old and the number of years practicing mean (SD) was 18 (13). Exploratory Factor Analysis identified four underlying constructs: (1) practice confidence (PC), (2) practice familiarity (PF), (3) practice attitudes (PA), and (4) methadone attitudes (MA). Statistically significant (p>.05) differences by race were observed for PC and PF; by ethnicity for PC; by pharmacy size for PF and PA; by gender for PF and MA; and by poverty for PA.
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Conclusions: Findings show this Brief (P-OUDP-Q) is a concise, multi-dimensional measure of Pharmacists perceptions on MOUD and Narcan, including distinct "stigma" dimensions, which is valid for use with Pharmacists in communities highly impacted by the opioid epidemic.
Financial Support: This research was supported by the National Institutes of Health (NIH) and the Substance Abuse and Mental Health Services Administration through the NIH HEAL (Helping to End Addiction Long-term℠) Initiative under award numbers UM1DA049394, UM1DA049406, UM1DA049412, UM1DA049415, UM1DA049417 (ClinicalTrials.gov Identifier: NCT04111939). Dr. Davis is supported by a career development award from the National Institute on Drug Abuse (K01DA044853).

ORAL SESSION: BUDDING INSIGHTS: HARNESSING ECOLOGICAL MOMENTARY ASSESSMENT TO EXPLORE THE MEDICAL FRONTIERS OF CANNABIS

Sweet ReLeaf? Daily Associations between Cannabis Use and Sleep among Young Adults who Report High-Intensity Alcohol Use

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Drug Category: Cannabis/Cannabinoids
Topic: Behavior
Abstract Detail: Other
Abstract Category: Original Research
Aim: Young adults often receive insufficient sleep durations and sleep disturbances are common among those who use alcohol and/or cannabis. Contemporaneously, cannabis legislation is expanding, perceptions of harm are declining, and using cannabis for sleep is widespread. Yet, whether cannabis actually improves or impairs sleep is unclear. This study tested reciprocal associations between cannabis use and sleep among young adults who reported past-month high-intensity alcohol use (8/10+ standard drinks for females/males).

Methods: Participants (N=204; M[SD]=22.08 years [2.78], 57% Female) completed 28 days of ecological momentary assessment (EMA). Morning reports assessed prior-day sleep (bed/wake times, subjective quality) and substance use (standard alcoholic drinks; tobacco [yes/no]; cannabis [yes/no, number of sessions on use days]). Multilevel models tested whether cannabis use related to better sleep quality and longer sleep durations that same day/night, and whether poorer sleep quality and shorter sleep durations related to next-day cannabis use. Covariates included age, sex, average cannabis use during the EMA period, day-level alcohol and tobacco use, study day, and day type (weekday versus weekend).
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Results: On average, participants reported alcohol and cannabis use on 12.09 (SD=5.73) and 6.87 (SD=8.67) days, respectively. Controlling for day-level alcohol use, cannabis use (versus non-use) was associated with longer sleep duration ($p<.05$), but not sleep quality. Number of cannabis sessions on use days was not related to same-day sleep. Sleep duration and quality did not predict next-day cannabis use or number of sessions on use days (ps GREATER THAN .05).
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Conclusions: Participants reported longer sleep duration, but not better quality, on days with cannabis use. However, more cannabis sessions did not result in longer sleep durations or better sleep quality. While cannabis may aid certain sleep behaviors, future research should examine how different cannabis quantities, timing of use, and formulations impact self-reported and objective sleep phenotypes among more diverse samples and across the lifespan.
Financial Support: NIAAA R01AA027495 (Merrill); P01AA019072 (Berey)

Beyond the Smoke: The Limited Ability of Cannabis to Predict Chronic Pain Relief

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Drug Category: Cannabis/Cannabinoids
Topic: Treatment, US Opioid Epidemic
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research
Aim: Challenges from the US opioid epidemic necessitate alternative analgesics for chronic pain management. Although cannabis demonstrated early promising effects on pain outcomes in trials, its effectiveness and risks in natural environments remain unclear. There is a need for ecologically valid, intensive longitudinal studies to support its clinical utility. We conducted smartphone-based ecological momentary assessments (EMA) to determine if cannabis predicts pain relief – thereby supporting its use as an alternative, non-opioid analgesic.
Methods: Participants (N = 133), who were patients with chronic pain (Age M = 42.6, 41% female, 63% Non-Hispanic White), completed up to four EMA surveys per day for 30 days (M = 78.22 average assessments; SD = 30.22; k = 10,091), assessing changes in their cannabis use and pain relief, defined as changes in pain ratings and milligrams of THC from the last EMA to the current one. We conducted curvilinear multiple regressions to predict pain relief, with changes in cannabis use and controlled for opioid use, route of administration, and demographic factors.
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Results: Participants reported regularly using edibles (M = 9.64mg THC between EMAs, SD = 11.51mg), $p>.001$, and smoking cannabis (M = 0.58mg, SD = 1.22mg), $p = .022$. Cannabis use predicted little variability in pain relief ($R2 = 1.10\%$), with no effect found for edibles, $p = .100$, nor inhalation, $p = .276$. We further adjusted for individual tolerance by using z-score deviations of cannabis use, and we found no effect for edibles, $p = .304$, or inhalation, $p = .365$.
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Conclusions: Although participants reported consistent cannabis use, cannabis did not predict pain relief in patients with chronic pain within their everyday, natural environments. The contrast between self-reported

cannabis consumption and the absence of measurable pain relief warrants future research on potential placebo effects and other psychological processes implicated in pain relief perception.
Financial Support: R21 DA048175; UM1 DA059000; T32 DA007292

Cannabis Use Among Sociodemographic-Diverse Cancer Patients at a South Florida NCI-Designated Cancer Center During Active Cancer Treatment

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Drug Category: Cannabis/Cannabinoids
Topic: Alternative Medicine
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research
Aim: Studies report an increase in cannabis use among cancer patients to manage symptoms such as pain, nausea, and appetite. However, there is dearth of research exploring the prevalence and patterns of cannabis use in cancer patients who consume cannabis during active treatment and those who did not use cannabis during active treatment.
Methods: Data is from a cross-sectional study of adult cancer patients seen at a National Cancer Institute (NCI)-designated comprehensive cancer center within the last 5 years. A harmonized survey was created with 11 other NCI centers to assess cannabis use patterns, source, and reasons for use. The survey was administered anonymously via RedCap. Descriptive statistics were calculated and stratified by +/-CDTX. Chi-squared/Fisher's exact tests where appropriate were conducted to compare proportions between groups.
Results: Among the sample (N=385) [49.5 years (SD 15.9); 53.0% male; 8.3% LGBTQ; 41.6% Hispanic/Latino], 41.0% consumed cannabis during active cancer treatment and 59.0% did not. Majority (71.8%) of respondents who consumed cannabis during active cancer treatment began cannabis consumption before diagnosis compared to 44.1% in respondents who did not consume cannabis during active cancer treatment ($p<0.0001$). Patients diagnosed with stage 4 cancer had a statistically significant higher prevalence (60.0%) of cannabis during active cancer treatment than non-use ($p=0.003$) Over half (53.3%) in radiation reported cannabis during active cancer treatment compared to 42.8% in chemotherapy, and 36.4% in immunotherapy. Over half (51.6%) of those who consumed cannabis during active cancer treatment did not have a "prescription" for cannabis. Depression, mood, and pain were the top 3 reasons for cannabis during active cancer treatment.
Conclusions: The prevalence and patterns of cannabis use differed between respondents who consumed cannabis during active cancer treatment compared to those who did not. Future studies should examine the physical and mental health impacts of cannabis use during and post-treatment.
Financial Support: NIMHHD T37MD008647; NCI P30CA240139-02S4

Evaluation of Antidepressant and Anxiolytic Effects of Medicinal Cannabis Use via Ecological Momentary Assessments

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Drug Category: Cannabis/Cannabinoids
Topic: Treatment
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research
Aim: Medicinal cannabis use to manage symptoms of anxiety and depression is common, despite mixed evidence for efficacy as a treatment for these symptoms and a dearth of longitudinal studies. The aim of this study was to examine changes in anxiety and depression over time among individuals with clinically significant anxiety and/or depression who were newly initiating medicinal cannabis use.

Methods: Adults (N=33; 20 women) with clinically significant anxiety or depression (Hospital Anxiety and Depression Scale (HADS) score< 8) were enrolled in this observational cohort study. Participants were newly initiating medicinal cannabis use in Maryland and had no more than 5 instances of cannabis use in the preceding six months. Assessments of depression, anxiety, sleep, pain, and functioning were completed at baseline and 1, 3, and 6 months after medicinal cannabis initiation. Ecological Momentary Assessment (EMA) measures were completed four times daily for 8 weeks after cannabis initiation with event-level mood measures (0-10 visual analog scale) collected prior to and immediately after each episode of cannabis use. Changes in anxiety and depression were evaluated using linear mixed effect models.
Results: Statistically significant decreases from baseline anxiety and depression were observed after initiating medicinal cannabis use ($p<.05$; d=0.67-1.16). The average HADS scores for anxiety and depression dropped below clinically significant levels by the three-month timepoint. Participants predominantly used THC-dominant cannabis products, and preferred route of administration varied. Acute reductions in anxiety (mean reduction=2.0; $p<.001$) and depression (mean reduction=1.3, $p<.001$) were reported after cannabis administration. Greater acute anxiety reductions were observed with smoked relative to oral or vaped products ($p<.001$) while route of administration did not change depression symptom reductions. Among oral products, approximately one standardized THC unit (~2.5-7.5 mg) produced the greatest anxiety reductions ($p=.004$) while approximately two standardized THC units (7.5-12.5 mg) trended towards producing the greatest depressive symptom reductions ($p=.08$).
Conclusions: Use of medicinal cannabis was associated with clinically significant decreases in anxiety and depression among individuals with moderate-to-severe anxiety or depressive disorders that was sustained over a 6-month period of observation. Acutely, the greatest changes in symptoms were observed at oral doses of one (5 mg) to two (10 mg) standardized THC units. Replication in controlled clinical trials and with well-characterized products are needed.
Financial Support: None

ORAL SESSION: PRIMM SINGLETON

The Role of Substance Use on ART Adherence Among Black People With HIV

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Drug Category: Other, Any historical substance use
Topic: Infectious Disease (e.g., HIV, HCV)
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research
Aim: Black people with HIV (PWH) show poorer rates of antiretroviral therapy (ART) adherence as well as poor psychosocial outcomes compared to other racial/ethnic groups in the U.S and may benefit from behavioral interventions. The iC-CHANGE (individual Community Care for HIV/AIDS Now: Getting Engaged) study evaluated the efficacy of a personalized, culturally adapted, text messaging intervention to improve ART adherence among Black PWH while also incorporating behavioral measures. This analysis sought to examine associations between substance use and quality of life (QoL).
Methods: Participants (90 Black PWH) were sent text messages through the individualized Texting for Adherence Building (iTAB) system, a personalized, two-way, fully automated text-messaging intervention. A measure of substance use (i.e., endorsement of specifically methamphetamine, cocaine/crack, and opioids use in the past five years) was administered at baseline. QoL was measured using the Medical Outcomes Study Short Form-36, which provides an indicator of overall health status with eight subscales. Multiple regression analyses were performed to explore the association between substance use and QoL, controlling for relevant covariates assessed at baseline (depression and age).
Results: The majority of the participants were male (82.0%), and mean (SD) age was 46.5 (11.7) years. Nearly half (48%) of participants endorsed previous substance use. Substance use was significantly associated with lower social functioning ($p<.001$) but no other QoL subscale ($p's< .05$). After accounting for covariates, the association between substance use and social functioning remained significant ($p<.001$). Among the variables

in the final model (model p<.001), higher depression symptomology and endorsement of substance use uniquely predicted poorer social functioning QoL (p<.001 and p=.02, respectively).
Conclusions: Among this sample of Black PWH, greater depressive symptomology and endorsement of substance use present barriers to social functioning QoL. Thus, treating mental health and substance use among this population is key to improving particularly social functioning QoL.
Financial Support: This work was supported by the California HIV Research Program (CHRP:HD15-SD-059).

Characterizing Patterns of Childhood Adversity in Association With Tobacco Cigarette Use Behaviors in Black Adults

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[1]*Johns Hopkins Bloomberg School of Public Health*

Drug Category: Nicotine/Tobacco
Topic: Environment/Stress
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research
Aim: There have been notable declines in tobacco cigarette use among US adults over several decades – an indication public health initiatives are working. However, some Americans continue to smoke despite the advances in tobacco control. There is strong evidence that childhood adversity is a determinant of tobacco cigarette use. Black individuals are more likely to experience adverse childhood experiences (ACEs), which may contribute to smoking in adulthood. The study aims to provide a comprehensive understanding of the interplay between early life adversity and tobacco cigarette use behaviors in Black adults.
Methods: Data are from the 2019 Behavioral Risk Factor Surveillance System (BRFSS). The analytic sample includes 14,685 adults aged 18 and older who identify as Black or African American from 21 states (62% women). We dichotomized ACE responses to indicate exposure and summed to create an ACE score. Indicators of childhood adversity were taken from BRFSS ACE Module. We used latent class analysis to identify ACE typologies and regression analyses to examine the association between the ACE classes and smoking status.
Results: Individuals reporting 4+ childhood adversity exposures were more likely to be a person who smokes (25.8%) compared to 16.9% of people who never smoked. More Black women reported childhood sexual abuse and more Black men reported verbal and physical child abuse. A four-class model had the most superior class fit for the data – (1) childhood sexual abuse (2) high adversity, (3) verbal abuse and parental divorce, and (4) low adversity. Current tobacco cigarette use was significantly more prevalent in the high adversity class compared to the other three classes (β=-0.214 (1v2) β=0.205 (2v3); p<0.001). Latent regression analyses stratified by gender found similar results.
Conclusions: We found different constellations of childhood adversity risk which may eventuate to tobacco cigarette use behaviors in adulthood. Our study identified that while exposure to a high number of childhood adversities was associated with current tobacco cigarette use, certain combinations of adversities were associated with more harmful tobacco use behaviors than others. We found children do not need to experience multiple childhood adversities to be at risk for tobacco use behaviors in adulthood – classes with fewer adversities also conferred risk of tobacco use behaviors in adulthood. The findings have the potential to inform the prevention and tobacco control interventions for Black adults who smoke.
Financial Support: NIH/NIDA Drug Dependence Epidemiology Training Program (T32DA007292)

Online Racism, Internalized Racism, and Alcohol Misuse among Ethnoracially Minoritized College Students.

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[1]*The New School,* [2]*Montclair State University*

Drug Category: Alcohol

Topic: Disparities
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research
Aim: Exposure to online racism is a growing problem among U.S. ethnoracially minoritized (EM) college students. Increased alcohol use during this developmental period is also a concern for EM young adults. In this study, we examined the association between online racism and alcohol use. We also investigated whether internalized racism mediated the association between online racism (i.e., individual or vicarious exposures) and alcohol use.
Methods: Participants included 494 EM college students ages 18-30 years (M = 19.62, SD = 2.08; 79% female; 60% Latine; 83% U.S.-born) from a Hispanic-Serving Institution in the Northeast U.S. who completed an online survey that included the Online Victimization Scale, AUDIT, and Cross Ethnic-Racial Identity Scale. The PROCESS macro in SPSS was used to test the direct effects of individual and vicarious online racism on alcohol misuse, as well as indirect effects through internalized racism. All models were adjusted for age and race/ethnicity.
Results: Findings revealed that individual (B =.13, SE = .05, p = .004) and vicarious (B =.10, SE = .04, p = .005) online racism were associated with increased alcohol misuse. The indirect association of online racism (i.e., individual and vicarious) on alcohol misuse via internalized racism was not statistically significant (personal: indirect effect = .01, SE =.01, 95% CI [-0.01, -0.04]; vicarious: indirect effect = .01, SE = .01, 95% CI [-.01, -.03]).
Conclusions: These findings underscore the impact of online racism on EM college students' mental health. Both individual and vicarious exposure to online racial discrimination was related to increased alcohol misuse. Internalized racism, however, did not help explain why this type of racism-related experience may confer risk for alcohol use. Results highlight the need for future studies to delineate the explanatory pathways between online discrimination and alcohol use.
Financial Support: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Drug Abuse. This research was supported by a grant from the National Institute on Drug Abuse (5R25DA035161-07, Multiple PIs: Ruglass and Hien) and by an early career grant from the Robert Wood Johnson Foundation.

Comparing Cardiovascular and Health Management Outcomes by Methamphetamine Use and Frequency in Men who Have Sex with Men (MSM)

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Drug Category: Stimulants
Topic: Substance Use Disorder
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research
Aim: This study evaluates associations and long-term effects of methamphetamine use on cardiovascular and health management outcomes among MSM with and at risk for HIV.
Methods: Survey data on substance use and objective cardiovascular measures were collected semi-annually from men enrolled in a cohort study based in Los Angeles, CA between August 2014-March 2020. Relationships between substance use and cardiovascular/health management outcomes were assessed using one-way Analysis of Variance (ANOVA) and fixed effects regression modeling.
Results: Participants included N=645 males aged 18-46 (mean: 35) years who were primarily Black (43%) or Hispanic (39%). Half the sample lives with HIV. About 85% reported substance use in the past 6 months and 37% reported methamphetamine, of which 11.1% used daily and 9.0% used weekly. One-way ANOVA revealed significant differences in BMI and waist-hip ratio across methamphetamine use frequency groups, with post-hoc analyses showing lower BMI and waist-hip ratio for weekly vs less frequent use. In fixed-effect regression modeling, daily methamphetamine use was associated with increased systolic blood pressure

(2.50mmHg (p=0.013)) compared with weekly or less. For those with HIV, daily (OR=0.31, 95%CI: 0.14-0.70) or weekly (OR=0.24, 95%CI: 0.11-0.52) methamphetamine use decreased odds of having a current prescription for HIV medication. Among them, presence (OR=3.52, 95%CI: 2.08-5.97) and frequency of methamphetamine use were associated with increased odds of missing 1+dose of HIV medication in the past week.
Conclusions: Frequency of methamphetamine use was associated with variations in cardiovascular indicators. Differences were noted between daily and weekly usage, suggesting that even modest reductions in use frequency may confer cardiovascular benefits and warrant further investigation. Methamphetamine use may pose unique challenges to health management, emphasizing need for targeted interventions to support care management in this population.
Financial Support: None

Depression Outcomes Among Women Participating in Worth Transitions

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Drug Category: Opiates/Opioids
Topic: Criminal Justice
Abstract Detail: Other
Abstract Category: Original Research
Aim: Women recently released from incarceration (WRRI) with substance use disorders (SUDs) are at an increased risk for developing or worsening depression symptoms due to stigmatization, a lack of access to quality treatment, and other comorbid individual, social, and structural risk factors. This study examines the change in depression symptoms by intervention exposure in WORTH Transitions (WT), a HIV/STI/HCV prevention and treatment program for women transitioning from incarceration with SUDs and HIV/STI/HCV risks that combines two evidence-based interventions: Women on the Road to Health (WORTH) and Transitions Clinic (TC).
Methods: WORTH is a structured, five-session intervention led by peer Community Health Workers with criminal legal system (CLS) histories, deemed efficacious in decreasing HIV/STI risk behaviors, intimate partner violence, and substance use among CLS-involved women. TC provides culturally-humble primary care and peer navigation services to WRRIs. TC is efficacious in improving health and retention in care. Participants were stratified by degree of exposure to intervention: no exposure, WORTH-only, TC-only, or WORTH+TC. Pre-post analyses included paired Wilcoxon signed-rank tests for depression measures at baseline and 6-months post-baseline. Substances used at baseline include opioids (29.1%) and cocaine (29.6%).
Results: Depression symptoms significantly decreased post intervention for WRRIs who participated in the intervention (p = .006). Additionally, WRRIs with severe depression were more likely to participate in each degree of exposure with WT, as compared to participants with moderate depression.
Conclusions: This study underscores the importance of WT on the mental health of CLS involved women with depression, substance use, and comorbid behavioral health needs. Future studies are needed to 1) examine what parts of WT were effective in decreasing depression; and 2) to characterize provider/client interactions and systems during the implementation of HIV/STI/HCV prevention programs like WT through the lens of implementation science.
Financial Support: None

Tuesday, June 18, 2024

ORAL SESSION: ALL (OK, SOME) WILL BE REVEALED: IMAGING IN ADDICTION RESEARCH

Endocannabinoid-Prefrontal Cortex Interactions during Inhibitory Control: Sex-Modulated Associations with Low-Level Substance Use in Preadolescents

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Drug Category: Other, Any use of one or more substances
Topic: Behavior
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research

Aim: Adolescence is a period of rapid development of both neurobiological frontal systems and risk-taking behaviors. Endocannabinoids (eCBs) play a role in this neurodevelopment and have been linked with executive functioning in adults. This study explored associations between ex vivo circulating eCBs, prefrontal (PFC) activation during inhibitory control, and downstream low-level substance use behavior in adolescents.
Methods: eCB concentrations [2-arachidonoylglycerol (2-AG) and an N-acyl ethanolamines (NAEs) factor] were quantified in serum from 177 preadolescents (ages 10-13; 40% female) using mass spectrometry. PFC regions of interest were extracted from fMRI blood oxygen level-dependent activation during inhibitory control (correct stop vs. correct go) on a stop-signal task. A structural equation model (SEM) was specified to investigate associations between eCBs, inhibitory PFC activation, and substance use (SU) in the next year. Paths were separately estimated for males and females; factor loadings and covariate regressions (age, parental history of substance misuse, and parental monitoring) were constrained to equality.
Results: The overall SEM fit the data well ($X^2(45)=52.190$, $p=.215$; CFI=.989; SRMR=.037; RMSEA =.030 [0,0.061]). Sex-specific regressions improved the fit: in females, paths between NAEs and PFC activation ($p=.045$), PFC activation and SU ($p=.002$), and 2-AG and SU ($p=.020$) were all significant, while non-significant in males. Higher 2-AG levels increased risk for SU in females, while higher NAE levels, partially-mediated through PFC activation ($p=.067$), decreased risk.
Conclusions: Our preliminary findings suggest differential sex effects of eCB subtypes on preadolescent substance use, which was partially-mediated through PFC activation during an inhibitory control task. The direction of some findings recorded here (2-AG, in particular) are inconsistent with past works, possibly suggesting sex by age interactions pertaining to eCB concentrations and their effects. Additional longitudinal research is needed to further clarify links between circulating eCB levels, neurocognition and unique SU risk pathways in males and females.
Financial Support: This research is supported by the National Institutes of Health under award numbers U01-DA041025 and R21-DA049109.

Cortical Functional Activation during Risky Decision-Making Associated to Youth Substance Use Initiation.

Paola Mattey Mora*[1], Olivia Murray[1], Joseph Aloi[1], Leslie Hulvershorn[1]

[1]*Indiana University School of Medicine*

Drug Category: Polydrug (i.e. concurrent use two or more drugs)
Topic: Neurobiology/Neuroscience, Epidemiology
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research

Aim: To determine the association between cortico-striatal activation during risky decision-making and initiation of risky substance use (RSU). We hypothesize differences with higher RSU initiation, particularly in cortico-striatal regions.
Methods: This cross-sectional study included a total of 141 substance-naive 11–12-year-old (at baseline) Indiana youth. Functional connectivity was recorded during the BART performance at baseline. Choose-inflate, choose-win, outcome-win, outcome-inflate, and outcome-explode contrasts were considered in the analysis. Regions of Interest (ROIs) were identified in areas that showed average activation differences between contrasts on a data subsample. Normalized fMRI data for these regions were analyzed in the remaining sample. Youth were monitored for RSU initiation over 5 years. Logistic-regression models were adjusted by SUD family history, externalizing behaviors, age initiation, sex, race, and parental education. Significance was determined at 95% confidence.
Results: Higher odds of RSU initiation were found in participants with one-unit increase activation during choose-inflate in the L-middle occipital gyrus (aOR=2.63, CI=1.45-5.34), and choose-win in the R-middle temporal gyrus (aOR=1.96, CI=1.12-3.73). Additionally, lower odds of RSU initiation were found in participants with one-unit increase activation during choose-inflate in the L-postcentral gyrus (aOR=0.25, CI=0.08-0.60), R-superior temporal gyrus (aOR=0.94, CI=0.11-0.63), middle temporal gyrus (aOR=0.49, CI=0.26-0.85), and middle frontal gyrus (aOR=0.51, CI=0.26-0.92); outcome-win in the L-middle occipital gyrus (aOR=0.46, CI=0.23-0.86); and outcome-inflate in the L-middle frontal gyrus (aOR=0.30, CI=0.12-0.68).
Conclusions: Activation for choose and outcome contrasts in cortical, but not striatal regions, related to low probability reward stimuli, behavioral inhibition, and reward anticipation, were associated with higher odds of RSU. This study shows the potential characterization of neural risk factors related to decision-making that are associated with RSU initiation. This characterization has implications in potential differentiated prevention and intervention development, that could consider risky decision markers. Further longitudinal studies are necessary to understand its implications with long-term substance use development.
Financial Support: This study is supported by the NIDA-grant: 5R01DA039764.

The Neurobehavioral Influence of Daily/Near Daily Cannabis Use on Value-Based Decision-Making

Miranda Ramirez*[1], Preston Tolbert[2], Joshua Beckmann[1], Joshua Lile[2], William Stoops[3]1 Michael Wesley[2]
[1]*University of Kentucky* [2]*University of Kentucky, College of Medicine,*

Drug Category: Cannabis/Cannabinoids
Topic: Imaging
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research
Aim: Dynamic decision-making involves the coordinated effort of multiple brain regions to guide future choices based on past experiences. Maladaptive decision-making is a key feature of cannabis use disorder, where individuals continue to use cannabis despite negative consequences. Reinforcement learning (RL) paradigms can be used to capture changes in the value of available options and may inform how the brain is impacted by cannabis use. This study combined fMRI with behavioral modeling of probabilistic choice task data to compare value-based decision-making between young adults reporting daily/near daily cannabis use (CAN:< 20 days/month) and controls (CTRL). We hypothesized that choice behavior and brain activity would differ between the groups.
Methods: Thirty-one CAN (age M±SD = 23.1 ± 4.7) and 31 CTRL (35.4 ± 8.7) participants were enrolled. Participants selected one of two options reinforced ($0.25) at independent reward probabilities that switched unpredictably. Behavioral data were analyzed using linear regressions, AIC model comparisons, and Wilcoxon Mann-Whitney U tests. Best-model derived value estimates were used in first-level GLMs to modulate brain activity at choice deliberation, and t-tests were used to compare whole brain extracted beta weights from FWE-corrected second-level analyses.
Results: CAN made fewer higher probability "rich" choices compared to CTRL ($F_{59}=39.06$, $p<.001$). A learning model including learning rate, inverse temperature, and perseveration parameters was the best model for both groups. CAN had lower inverse temperature ($U=112$, $p<.001$) parameter estimates, indicative of a

lower likelihood of using current option value to inform choice. fMRI analyses demonstrated greater value-modulated activity in the left superior medial lobe (t59=2.00, p=0.023) and the left OFC (t59=2.00, p=.045) for CAN compared to CTRL.
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Conclusions: These results demonstrate more disadvantageous choices and hyperactivity in regions implicated in reward learning in people reporting daily/near daily cannabis use, which reveals a potential mechanism for maladaptive decision-making in cannabis use disorder.
Financial Support: K01DA043652, R01DA045023, R01DA047368, and T32DA035200

Drug Use Severity is Linked to Reduced Brain Network Segregation in Opioid Use Disorder

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Drug Category: Opiates/Opioids
Topic: Neurobiology/Neuroscience
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research
Aim: The brain is organized into large-scale networks of functionally connected brain regions. In the healthy brain, networks are "segregated," meaning that neural communications within a network are stronger than communications between networks. However, network segregation is reduced in cognitive impairment and aging. We hypothesized that recent drug use severity in opioid use disorder (OUD) might also be linked to reduced network segregation.
Methods: Forty adults with OUD completed resting-state fMRI and the Addiction Severity Index (ASI). We grouped 264 brain regions into 10 networks, categorized as “association” (i.e., supporting higher-order cognition) or “sensorimotor” (i.e., sensory and motor) networks. Network segregation was defined as the strength of correlations among regions within the same network compared to correlations among regions in distinct networks. Two hierarchical regressions examined the unique and interacting effects of ASI drug use severity (past 30 days) and age on association or sensorimotor network segregation. Analyses used percentile bootstrapping and Bonferroni correction ($\alpha = .025$).
Results: Association networks: ASI predicted lower segregation (B = -.43, p = .006), while neither Age (B = -0.26, p = .046) nor ASI*Age interaction (B = -.17, p = .27) predicted segregation. Sensorimotor networks: ASI did not predict segregation (B = -.12, p = .45), but Age predicted lower segregation (B = -.47, p = .004) and the ASI*Age interaction was marginally significant (B = 0.39, p = .027). Marginal means showed Age predicted lower sensorimotor segregation at -1SD ASI (B = -.80, p> .001) but not at +1SD ASI (B = .002, p = .52).
Conclusions: More severe drug use in patients with OUD is related to lower brain network segregation among the higher-order association networks but not the sensorimotor networks. Reduced efficiency in inter-region communication within association networks may contribute to or characterize the cognitive impairment and accelerated brain aging seen in OUD.
Financial Support: NIH/NIDA T32DA028874 (Hager, Post-Doc Fellow); Commonwealth of Pennsylvania C.U.R.E. Addiction Center of Excellence: Brain Mechanisms of Relapse and Recovery (Childress)

ORAL SESSION: PRECLINICAL STUDIES OF DRUG WITHDRAWAL

Body Weight Loss as a Biological Indicator of Fentanyl Withdrawal Severity when Xylazine is Self-Administered as a Fentanyl Adulterant in Rats

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Drug Category: Opiates/Opioids
Topic: Substance Use Disorder
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research
Aim: Evaluated the impact of fentanyl+xylazine co-use and withdrawal on body weight and severity of the fentanyl withdrawal syndrome in rats.
Methods: 32 Long Evans rats underwent jugular vein catheter surgery followed by 10 sessions of 2h fentanyl SA. Rats were then assigned to fentanyl alone, fentanyl+xylazine, or fentanyl+lofexidine SA. Rats then underwent withdrawal symptomology recording. Bodyweight was recorded throughout experimental timeline. Analysis included linear mixed effects modeling and areas under the curve.
Results: Rats in all groups lost roughly 15% body weight throughout experimentation, with no group differences. Linear mixed effects modeling was conducted on the weight difference from the 0 to 24 h withdrawal timepoint, which indicated a significant main effect of group ($F_{2,27}= 6.49$, $p<0.05$), with post-hocs indicating that only the fentanyl+xylazine group lost significantly more weight versus the fentanyl alone group. Change in weight was also correlated with the change in somatic signs of withdrawal ($R2=0.17$, $p<0.05$).
Conclusions: These results demonstrate that the fentanyl+xylazine combination induces greater weight loss during acute fentanyl withdrawal and is related to acute fentanyl withdrawal severity. Translationally, these results suggest that body weight loss during acute withdrawal may be an important biological indicator of severity of the withdrawal experience.
Financial Support: Supported by the National Institute on Drug Abuse grant R01 DA058933 (to CDG and TDH), R01DA046526, R33 DA049130, R21 DA055879 (to CDG). Commonwealth Undergraduate Research Experience from the Substance Use Research Priority Area at the University of Kentucky.

A Putative Role of the Neuroimmune System in Heroin Withdrawal

Nadia Said*[1]

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Drug Category: Opiates/Opioids
Topic: Behavioral Pharmacology
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research
Aim: Over the last two decades, opioid overdose has become the leading cause of accidental deaths in the United States, causing nearly 500,000 deaths from 1999 to 2019. Recent evidence suggests that glial activation and the related neuroimmune signals may be involved in the dependence-inducing properties of opioids. Although some treatments, like methadone buprenorphine naltrexone or naloxone, have proven effective, relapse rates remain high. Therefore, the identification of new non-opioid targets for the treatment of OUD is urgently needed. The main purpose of this study is to investigate the role of neuroimmune systems in opioid withdrawal-related behavior in rats.
Methods: We first measured hyperalgesia and the aversive effects of heroin withdrawal in adult male (n=22) and female (n=23) Wistar rats. Hyperalgesia was assessed using the von Frey and Hargreaves tests, for mechanical and thermal sensitivity, respectively, after two weeks of repeated heroin administration. We also investigated the heroin withdrawal-induced conditioned place aversion (CPA) and naloxone-precipitated somatic withdrawal. Then, we quantified 17 cytokines and chemokines in whole brains of both saline- and heroin-treated rats by a FirePlex immunoassay.
Results: The data showed that two chemokines (CCL2 and CXCL1) and a cytokine (IL-10) were significantly upregulated in male rats that received heroin but not in females. Based on these results, we investigated whether an acute injection of a CCL2 antagonist could reverse the heroin-induced hyperalgesia, CPA and somatic withdrawal symptoms in heroin-dependent male (19) and female (20) Wistar rats. Results showed that the antagonist significantly reversed mechanical and thermal hyperalgesia, and attenuated CPA and somatic withdrawal symptoms in males and females.

Conclusions: In summary, our findings suggest a sex-dependent proinflammatory effect of heroin withdrawal in the rat brain and that CCL2, CXCL1 and IL10 may be involved in the etiology of OUD. Our data also shows that CCL2 may contribute to motivational and somatic signs of opioid withdrawal in both male and female Wistar rats. Together, these investigations might lead the discovery of novel neuroimmune targets, such as chemokine antagonists, for opioid dependence and contribute to medication development for OUD.
Financial Support: NIDA/NIH

Selective Antagonism of Interpeduncular Nucleus α3β2* and α6β2* Nicotinic Acetylcholine Receptors Reduces Nicotine Withdrawal in High Withdrawal Expressing Female Long Evans Rats.

Darlene Brunzell*[1], Romi Balasubramanian[1], Elizabeth Geisler[2], J. Michael McIntosh[2], Paul Whiteaker[1]

[1]*Virginia Commonwealth University, University of Utah*

Drug Category: Nicotine/Tobacco
Topic: Behavioral Pharmacology
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research
Aim: Each year nearly 20 million individuals attempt unsuccessfully to quit smoking. Recent studies in smokers highlight variations in individual nicotine withdrawal (NICWD) symptoms, identifying those with greatest NICWD as most vulnerable to relapse. Rodent models of somatic NICWD have predictive validity for tobacco cessation efficacy and enable systems-level assessment of nicotinic acetylcholine receptor (nAChR) contributions to NICWD. The interpeduncular nucleus (IPN) is well-known to support NICWD, but the contributions of the α3β2* and α6β2*nAChR subtypes enriched there, have not been rigorously examined (*denotes other possible subunits). Mecamylamine-precipitated NICWD procedures have concluded that β2*nAChRs play no role. Utilizing spontaneous NICWD and parsing subjects based upon NICWD severity, better models the human condition and enables testing an alternative HYPOTHESIS that IPN α3β2* and/or α6β2*nAChR activation increases NICWD behavior.
Methods: Female Long Evans Rats (n=17) were surgically implanted with guide cannula 2mm dorsal to the IPN target to enable local IPN and anatomical-control infusion of antagonists selective for α3β2*nAChRs (CTXPeIA), α6β2*nAChRs (CTXH9A) or both α3β2*/α6β2*nAChRs (CTXMII) in nicotine-naïve and spontaneously withdrawn rats (24h replacement of 25 µg/mL nicotine in 2% saccharin solution with H20). 0, 5 and 10 pmol CTX was infused using a within-subject, Latin Square design.
Results: Rats showed elevated somatic NICWD scores following nicotine removal (96.18±9.16) compared to naïve state (64.12±7.8; p=.003) and NICWD positively correlated with nicotine intake (r=.63, p=.022). Parsing rats according to WD score (low> ACSF and high ≥ mean ACSF WD) revealed that IPN infusion of CTXPeIA, CTXH9A and CTXMII significantly reduced WD measures in high NICWD rats (p's LESS THAN .05). There was no effect of CTX infusion in low NICWD rats, naïve rats or following anatomical-control infusions (p's > .05).
Conclusions: These data suggest that activation of IPN α3β2*/α6β2*nAChRs supports NICWD behavior and identify antagonism of α3β2* and α6β2*nAChRs as a novel strategy to alleviate NICWD in smokers.
Financial Support: This work was supported by NIH Grant R01DA042749.

Effects of Repeated Oxycodone Administration and Abstinence on Behavior and Extracellular Matrix Structures in Male and Female Wistar Rats

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Drug Category: Opiates/Opioids
Topic: Neurobiology/Neuroscience
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research

Aim: The nonmedical use of oxycodone, a potent and commonly prescribed opioid analgesic, can cause addiction and dependence. We hypothesized that male and female subjects exposed to repeated injections of oxycodone would exhibit tolerance and dependence-like effects and that abstinence would alter expression of specialized extracellular matrix proteins (e.g. perineuronal nets) that are implicated in neuroplasticity and drug-related conditioning.
Methods: Adult male and female Wistar rats (~10 weeks old) were randomly assigned to groups that received acute or repeated injections (twice daily for 7 days) of oxycodone (2 or 4 mg/kg, i.p.) or 0.9% saline vehicle. Thermal antinociception (i.e. tail withdrawal test) was used to validate acute opioid intoxication, tolerance, and spontaneous or precipitated withdrawal, following a naloxone (1 mg/kg, i.p.) injection and after an acute or extended (1 day vs. 4 week) abstinence interval. Behavioral testing included marble burying, elevated plus maze, and an opioid withdrawal rating scale. Serial collection of whole-brain coronal slices and immunohistochemistry were used to identify Wisteria Floribunda Agglutinin (WFA)-positive perineuronal net structures.
Results: Results showed significant acute antinociceptive effects of oxycodone in both male and female rats (increased latency in the tail withdrawal test), as well as tolerance following repeated injection ($p > 0.05$). Withdrawal rating scores were not significantly different between repeated oxycodone injection and control groups, and naloxone did not increase withdrawal rating scores. However, marble burying behavior was significantly higher following naloxone injection in subjects that received repeated oxycodone injections. Preliminary data suggest possible changes in perineuronal net count and intensity in cortical and hippocampal regions following abstinence to oxycodone administration.
Conclusions: Overall, these data confirm that oxycodone administration and abstinence in male and female rats may alter extracellular matrix structures integral to neuroplasticity-related learning and memory, with or without behavioral tolerance or withdrawal-like effects. Ongoing experiments will determine possible effects following repeated fentanyl intoxication.
Financial Support: Supported by NIH Grant DA047413

ORAL SESSION: LICIT AND ILLICIT USE OF PSYCHEDELICS

Latent Class Analysis of Changes in Substance Use and Depressive Symptoms following Naturalistic Psilocybin Use: Results from a Prospective Longitudinal Survey

Jeremie Richard*[1], Sandeep Nayak[2], Nathan Sepeda[2], Albert Garcia-Romeu[1] [2]*Johns Hopkins University,* [1]*Johns Hopkins University School of Medicine*

Drug Category: Psychedelics
Topic: Behavioral Pharmacology
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research
Aim: The classic psychedelic psilocybin, found in certain mushroom species, is receiving renewed interest in naturalistic and clinical research settings. Despite trends indicating increased rates of use outside of research settings, data on the public health impact of psilocybin use remains limited.
Methods: A prospective longitudinal study comprising six sequential surveys from adults planning to take psilocybin outside of clinical settings. Data was collected at consent (T1), two weeks before (T2), one day before (T3), one to three days after (T4), two to four weeks after (T5), and two to three months after (T6) psilocybin use. 2,833 respondents (54% male, 46% female) completed baseline assessments and 657 completed final follow-up. A latent class analysis of changes in depressive symptoms (BDI-II), alcohol use problems (AUDIT) and drug use problems (DUDIT) from T2 to T6 was conducted to identify patterns in response to psilocybin. Comparisons between classes were conducted based on sociodemographic and psychological characteristics.
Results: Based on optimal model fit indices, six classes were identified representing differing degrees of depressive and substance use symptom change following psilocybin use. A majority of respondents reported improvements in depressive symptoms (81.2%). Three classes reported improvements in depressive symptoms and alcohol use problems (6.6%), drug use problems (6.1%), and alcohol/drug use problems

(0.8%). Two classes reported a worsening of alcohol use problems (4.1%) and a worsening of drug use problems (1.2%). The classes with the most severe depression and alcohol/drug use reported greater trait neuroticism (p = .01), trait anxiety (p> .01) and poorer cognitive flexibility (p> .01) at T2, with these differences becoming non-significant (p< .05) at T6.
Conclusions: Although psilocybin use resulted in positive psychological changes for the majority of respondents, a minority experienced a worsening of symptoms. These findings are in line with results from other naturalistic studies and clinical trials indicating the therapeutic potential of psilocybin, yet also acknowledges the potential harms without adequate screening, preparation, and support.
Financial Support: None

Collecting Abuse-related Adverse Event Information in Clinical Trials of Psychedelics and Novel Psychoactive Drugs to Inform Scheduling and Labeling: Issues, Methods, and Recommendations

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[1]*Pinney Associates,*

Drug Category: Psychedelics
Topic: Other, Abuse Potential Assessment
Abstract Detail: Clinical - Experimental
Abstract Category: Theoretical/Commentary
Aim: Assessing the abuse potential (AP) of CNS-active drugs during development requires the evaluation of data from numerous sources, including nonclinical and clinical studies. Per FDA's 2017 AP guidance, a full AP assessment (APA) includes identifying potentially abuse-related adverse events (ARAEs) in all safety and efficacy clinical trials. Psychedelics and novel drugs that produce ambiguous signals in nonclinical and clinical AP studies provide unique challenges to the APA, and thus particular focus on ARAE assessment methods is paramount. This presentation will summarize the issues involved with assessing ARAEs and methods and recommendations for collecting ARAE data that will inform the APA and scheduling recommendation to be submitted with the New Drug Application and provide the data FDA will need in its Controlled Substances Act scheduling recommendation and labeling development.
Conclusions: Psychedelics and novel drugs may produce profound psychoactive effects that could be associated with the therapeutic response; however, these events should be collected and reported as ARAEs. Proper ARAE assessment requires a well-planned prospective, systematic methodology, starting with a prespecified list of ARAEs that will be closely monitored as events of special interest. Terms related to euphoria, dissociation/psychosis, intoxication, CNS stimulation or depression, and others specific to the drug type or class should be included. Investigators and staff must be trained to identify and record information about ARAEs when they occur so that detailed narratives can be written. Comprehensive narratives provide contextual information and help determine if psychoactive effects of the drug (e.g., hallucinations, euphoria, sedation) appear likely to motivate post-treatment recreational use or are instead aversive and unlikely to be sought out. Since no clear objective criteria for such differentiation exist, collecting detailed contextual information and summarizing ARAE data in a clear and thorough manner will better inform the Sponsor and FDA and assist in scheduling and labeling decisions.
Financial Support: This work was funded by Pinney Associates, which provides scientific and regulatory consulting to support the clinical development of a broad range of CNS active substances and drug products including new chemical entities and alternative formulations and routes of delivery.

Prevalence of Use of Psilocybin and MDMA in Multiple US Cities

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Drug Category: Psychedelics
Topic: Epidemiology
Abstract Detail: Clinical - Epidemiology

Abstract Category: Original Research
Aim: Amid rising media coverage of psychedelics for personal transformation, both the classic psychedelic psilocybin and MDMA/ecstasy are currently the focus of Phase III clinical trials for treatment of depression and PTSD. There are few epidemiologic studies that have examined recent use in the general population.
Methods: Since November 2021, the National Drug Early Warning System (NDEWS) has conducted field studies in 20 US cities on a monthly basis through its Rapid Street Reporting (RSR) study, to conduct anonymous surveys about drug use in the community. On weekends in each city, respondents were recruited using a street- and venue-intercept method. Each adult participant was asked about past 12-month use of ~100 drugs, including common psychedelics such as psilocybin/shrooms and MDMA/ecstasy. A total of 6122 surveys were completed across 24 site visits as of December 2023.
Results: Although reported use of these substances varied substantially across cities, psilocybin emerged as one of the most commonly reported substances in the past 12 months. Past-year use ranged from 3.6% to 37.6% (mean: 13.7%). In 19 out of 24 site visits, psilocybin was in the top five most frequently reported drugs, and in 9 of the visits it was the third most commonly reported substance, after alcohol and recreational cannabis. Reported use of MDMA varied from 2.0% to 17.1% (mean: 6.5%) and was one of the ten most commonly reported substances in 14 visits.
Conclusions: Although RSR is not a prevalence study, NDEWS surveillance efforts revealed noteworthy prevalence of use of select psychedelics, especially psilocybin. Considering the burgeoning research on the use of these substances for multiple mental health conditions, along with decriminalization efforts, it is critical to understand the growing use outside the health system, as documented by the RSR study, in order to focus harm reduction efforts.
Financial Support: The National Drug Early Warning System is supported by a cooperative agreement with NIDA, U01DA051126. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Clinical Trial Comparing Psilocybin to Nicotine Patch for Tobacco Addiction

Matthew Johnson*[1]

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Drug Category: Psychedelics
Topic: Treatment
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research
Aim: Annual tobacco smoking-related deaths are estimated at 480,000 in the US and 5 million worldwide, dwarfing mortality for all other drugs of abuse. Most behavioral interventions and pharmacotherapies for smoking cessation result in only modest long-term success rates. A small pilot study published in 2014 found that among 15 treatment-resistant smokers, a program combining psilocybin with cognitive behavioral therapy resulted in very high success rates (e.g., 7-day point prevalence abstinence rates of 80% at 6-months after the target-quit-date). The aim of the present study was to test psilocybin treatment versus a well characterized smoking cessation treatment (nicotine patch) in a randomized clinical trial, with the hypothesis that the psilocybin group would show greater abstinence rates at 6-months follow-up.
Methods: This completed comparative efficacy study randomized 82 treatment-resistant tobacco cigarette smokers (male and female) to either a single 30 mg/70 kg psilocybin session (n=42) or FDA-standardized nicotine patch treatment conditions (n=40). Both groups received an identical 13-week cognitive behavioral therapy program for smoking cessation. For the psilocybin group, psilocybin sessions occurred on the target-quit-date and involved an introspective "psychedelic therapy" framework, whereas cognitive behavioral therapy took place in meetings before and after the psilocybin session day. Smoking status was assessed using breath carbon monoxide (CO), urinary cotinine, and self-report 6 months after the target-quit-date.
Results: Participants had the following baseline demographics, which did not statistically differ between groups: mean age 48 years, mean of 16 cigarettes smoked per day, mean of 8 previous quit attempts, 40% female, and 89% White. At the 6-month follow up, 22 (52.4%) participants in the psilocybin group were biologically verified as abstinent (7-day point-prevalence), compared to 10 (25.0%) in the nicotine patch group. Binary logistic regression indicated participants in the psilocybin group were more than 3 times as likely to be abstinent than the nicotine patch group at the 6-month follow up, which was a statistically

significant difference (b = 1.19, SE b = 0.48, OR = 3.30 [95% CI = 1.29 – 8.43], p = .013). No serious adverse events were attributed to psilocybin or nicotine patch treatment.
Conclusions: A single psilocybin session, compared to nicotine patch treatment, in the context of a cognitive behavioral therapy program, significantly and substantially increased long-term tobacco abstinence. Abstinence rates were substantially higher than those typically observed in smoking cessation treatment. Psilocybin therapy holds strong promise for tobacco smoking cessation, and should continue to be tested for approval by FDA and other regulatory agencies.
Financial Support: Heffter Research Institute, William Harrison

ORAL SESSION: BREAKING DOWN BARRIERS: ADDRESSING DISPARITIES IN SUBSTANCE USE AMONG JUSTICE-INVOLVED POPULATIONS

Transitions of Care between Jail-Based Medications for Opioid Use Disorder and Ongoing Treatment in the community: A Retrospective Cohort Study

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Drug Category: Opiates/Opioids
Topic: Criminal Justice
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research
Aim: Offering medications for opioid use disorder (MOUD) in carceral settings significantly reduces overdose risk. However, it is unknown whether and to what extent individuals in U.S. jail settings continue MOUD once they leave incarceration. In this study, we aimed to assess the relationship between in-jail MOUD receipt and MOUD utilization in the month following release among a multi-year cohort of individuals incarcerated at the NYC jail, and identify individual factors associated with treatment discontinuity.
Methods: We conducted a retrospective cohort study of linked NYC jail-based electronic health records and community Medicaid OUD treatment claims for individuals with OUD discharged from jail to the community between May 1, 2011 and December 31, 2017. We compared receipt of community-based MOUD within 30 days of release, among those with and without MOUD at release from jail. We tested for effect modification based on MOUD receipt prior to incarceration and assessed factors associated with treatment discontinuation following release.
Results: Of 28,298 eligible incarcerations, 52.8% received MOUD at release. 30% of incarcerations with MOUD had a community-based MOUD claim within 30 days of release, compared to 7% of incarcerations without MOUD (Risk Ratio: 2.62 (2.44-2.82)). Most (69%) of those with MOUD claims prior to incarceration who received in-jail MOUD continued MOUD in the community, compared to only 9% of those without prior MOUD. Among incarcerations with MOUD at release, those who were younger, Non-Hispanic Black and with no history of MOUD treatment were less likely to continue treatment following release.
Conclusions: MOUD maintenance in jail is strongly associated with MOUD continuity upon release. Still, findings highlight a continued gap in MOUD upon-reentry, especially among those who initiate MOUD in jail. In the wake of worsening overdose deaths and troubling disparities, improving continuity of evidence-based care among this population must be an urgent policy priority.
Financial Support: NIDA R01DA045042-01A1; NIDA K01DA055758 (Krawczyk)

Who Gets Treatment And Who Gets Criminalized Racialized Associations Between Cannabis Arrests And Criminal Legal System Referrals To Cannabis Treatment, 1992-2019

Pia Mauro*[1], Erin Annunziato[1], Ruth Shefner[1], John Pamplin II[1], Seth Prins[1]

[1]*Columbia University*

Drug Category: Cannabis/Cannabinoids
Topic: Criminal Justice
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research

Aim: Black racialized people are more likely to be arrested for cannabis than their white racialized counterparts despite no difference in cannabis use. While arrests could connect people with cannabis use disorder to treatment, we tested whether cannabis arrests could perpetuate disparities in care through racialized treatment referrals.
Methods: We used data from the Treatment Episode Data Set (1992-2019) and the Uniform Crime Reporting Program Arrests sex-race series (1991-2018). We estimated race-specific rates of cannabis treatment criminal legal system (CLS) referrals (including cannabis treatment admissions listing cannabis as a primary/secondary/tertiary problem substance) and cannabis arrests (possession and sale) per 100,000 people by state/year. We regressed cannabis treatment CLS referrals on cannabis arrests (lagged 1 year) using negative binomial models with state and year fixed effects, and tested racialized differences (Black, white, Asian) using interaction terms.
Results: Across state-years, average cannabis arrest rates were 568.4 among Black people, 174.4 among white people, and 55.1 among Asian people. Cannabis treatment CLS referral rates were 267.6 among Black people, 85.6 among white people, and 35.6 among Asian people. A 10% increase in cannabis arrest rates was associated with a 1% increase in the cannabis treatment CLS referral rate among white people (i.e., aIRR=1.009, 95% CI=1.002, 1.016) and a 3% increase among Asian people (i.e., aIRR=1.028, 95% CI=1.023, 1.033), but not among Black people (i.e., 1.001, 95% CI=0.996, 1.006). Associations were significantly stronger for white and Asian people than Black people.
Conclusions: Despite their disproportionate cannabis arrest burden, Black people were the only group among whom arrests were not associated with cannabis treatment CLS referrals, indicating ongoing criminalization without improved treatment access. Racialized differences in the association between cannabis arrests and cannabis treatment CLS referrals provide a mechanism through which the criminal legal system contributes to cannabis-related treatment disparities.
Financial Support: R01DA055606, K01DA045224, K01DA045955, K01DA058085, T32DA031099

The Continuing Care Mobile Application for Justice-Involved Individuals With Substance Use Disorders: Findings From an Initial Randomized Trial

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Drug Category: Opiates/Opioids
Topic: Technology (e.g., mHealth)
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research

Aim: Justice-involved populations have high prevalence of substance use disorders (SUDs) and are at heightened risk of overdose mortality in the community. We describe the development and initial evaluation of the prototype Continuing Care (CC) mobile application – a self-guided, interactive digital intervention designed to meet the recovery and personal support needs of justice-involved individuals with SUDs.
Methods: The CC app was developed through an iterative, research-driven process and uses motivational language and cognitive behavioral principles. App content drew from and expanded upon an empirically-supported manualized intervention for justice-involved populations. One hundred adults (56% male, 58% Black) with SUD and a lifetime history of justice involvement were recruited from an Opioid Treatment Program in Baltimore, USA. Participants were randomized to the CC app (n=50) or Control (no app; n=50) for 12 weeks, in addition to standard outpatient treatment. Assessments and urine testing were conducted at baseline, 6-, 12-, and 18-weeks.
Results: Engagement was high among participants in the CC arm, with 61.7% using the app on 4 or more days of a typical week during the 12-week trial. Mean (SD) satisfaction scores (on a 1-10 scale) were 8.5 (1.3), and 96% reported being willing to continue using the app after the trial. Treatment program retention at 12-

weeks did not differ significantly (94% CC vs. 82% Control; p=0.08), but participants in the CC arm were less likely than participants in the Control arm to test positive for non-treatment opioids at 12-weeks (53% CC vs. 74% Control, p<0.05). There were no significant differences in self-reported drug use or criminal activity.
Conclusions: Findings from this small randomized trial suggest that the CC app holds promise for engaging vulnerable justice-involved individuals and may reduce opioid use. The CC app is currently undergoing additional enhancement and evaluation as part of ongoing NIH-supported research.
Financial Support: NIMHD 5R44MD008848

Incarceration and Fatal Opioid Overdoses, Connecticut, 2015-2021

Kaylia Carroll*[1], Russell Barbour[1], Grau Lauretta[1], Sandra Violette[2], Robert Heimer[1]

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Drug Category: Opiates/Opioids
Topic: Criminal Justice
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research
Aim: For individuals with opioid use disorder, the period following release from incarceration carries a high risk of opioid overdose and death. While multiple studies have focused on the risk in the period immediately following release, less is known about how risk declines as the time since release elongates. This study seeks to close this gap.
Methods: We conducted a retrospective study linking overdoses in Connecticut during 2015-21 to prior incarceration. Deaths with opioid involvement were identified by the Office of the Chief Medical Examiner (N=7,306). Using name, date of birth, sex, and race/ethnicity, deaths were linked to Department of Correction records, which provided the release date closest to the date of death. We determined the percentage with a history of incarceration and compared demographic characteristics and geographic site of injury to those without a history of incarceration. For those with a history of incarceration, we assessed the interval between release and death.
Results: There were 7,306 opioid-involved accidental deaths during the seven-year observation period. Half of the decedents (50.0%) had a history of incarceration; the proportion was lower for women (36.2 % vs 54.6% for men, p<0.0001) and higher for Blacks (65.5% vs. 48.2% for all others, p<0.0001). Overall, the site of injury for 79% of decedents was a private residence, but the proportion was lower for those with a history of incarceration (76% vs 82%, p<0.001). Fourteen percent of decedents with a history of incarceration died within one year of release, but 4.3% did so within one week.
Conclusions: A history of incarceration is common among those who died of an opioid overdose. Most noteworthy, 4% of all such deaths were in first week following release. More efforts are needed to reach newly released individuals to reduce the chances of a fatal overdose.
Financial Support: Supported by a grant from the CDC -- 1 NH28CE003554-01

ORAL SESSION: BREATHING MATTERS: OPIOIDS AND RESPIRATION

Pharmacological and Physiological Differences between Synthetic Opioids and Morphine at the Upper Airway

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Drug Category: Opiates/Opioids
Topic: Mechanisms of Action
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research

Aim: According to the Centers for Disease Control, fentanyl is currently the most common cause of overdose death in the U.S despite the widespread availability of naloxone. These deaths continue to rise while the death rate from heroin (diacetylmorphine) is relatively unchanged. Fentanyl causes sustained vocal cord closure (VCC), whereas it is unclear whether morphine does the same. Therefore, the aims of this study were to: (1) compare the time and dose relationships between morphine and fentanyl on VCC; and (2) evaluate the time-course and dose-range interaction of naloxone treatment on VCC reversal.
Methods: We used an established fentanyl overdose model in Sprague-Dawley rats with fiber-optic endoscopy to observe the VC activity effects of fentanyl, morphine and naloxone. Rats were also instrumented to monitor blood pressure, heart rate and respiration rate.
Results: Fentanyl was injected IV at seven different doses (5-100 ug/kg, n = at least 6 animals/dose). At the 5-20 ug/kg doses, VC activity ranged from transient fluttering to prolonged closure occurring approximately 20 seconds after injection. At the 25 ug/kg dose, VCC occurred within 10 seconds of injection and was sustained for 2 minutes. At all doses of morphine (IV; 5 different doses (2.5-12.5 mg/kg, n = at least 6 rats/dose), only brief VC fluttering was observed. We also evaluated the ability of a range of doses of naloxone (IV; 150-2000 ug/kg) to reverse fentanyl (25 ug/kg)-induced VCC. VCC could be reversed by naloxone, but only when administered within 30 seconds of fentanyl injection. When naloxone was delivered 45 seconds or 60 seconds after fentanyl delivery, VCC was rarely reversed.
Conclusions: These studies have significant implications for drug development and future therapeutic strategies for drug overdose treatment involving fentanyls.
Financial Support: NIH grants to RT: R41DA055409 and R44DA056267. VA Senior Research Career Science Award RCSR-008-21S to AJ.

Suvorexant Enhances Oxycodone-Induced Respiratory Depression in Male Rats

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Drug Category: Opiates/Opioids
Topic: Drug Interactions
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research
Aim: Recent studies have proposed the use of dual orexin receptor antagonists, such as suvorexant (Belsomra®), for the treatment of opioid use disorder (OUD) and related sleep disturbances because of orexin's role in sleep-wake regulation and potential role in addiction. Accumulating evidence suggests that orexin is also an important modulator of respiratory function, raising the possibility of adverse interactions between therapeutic orexin antagonists and opioids on respiration. The aim of the present study was to investigate the effects of suvorexant, alone or in combination with the opioid oxycodone, on pulmonary ventilation in male rats.
Methods: Adult, male Sprague Dawley rats received treatments with vehicle, oxycodone (3 and 10 mg/kg, i.p.) or suvorexant (10 and 18 mg/kg, i.p.). Doses of suvorexant were chosen based on studies showing that doses of 10-30 mg/kg significantly promote sleep, and 20 mg/kg significantly blocks oxycodone self-administration in rats. Respiratory measures were obtained using whole-body plethysmography. We then tested the effects of a combination of suvorexant (10 and 18 mg/kg, i.p.) and the highest dose of oxycodone that did not suppress respiration (3 mg/kg, i.p).
Results: Our results show that oxycodone dose-dependently induced respiratory depression, with the highest dose tested (10 mg/kg) significantly decreasing minute volume (mls/min) and tidal volume (mls). Suvorexant alone did not alter respiratory measures at the doses tested in the present study. A combination of 18 mg/kg (but not 10 mg/kg) suvorexant with an ineffective dose of oxycodone (3 mg/kg) significantly decreased minute volume, tidal volume and respiratory frequency compared with vehicle and either drug alone.
Conclusions: Our findings showed that suvorexant, at a dose associated with sleep promotion and blockade of oxycodone self-administration, robustly enhanced oxycodone-induced respiratory depression in male rats. These results raise the possibility that orexin antagonists may worsen respiratory-depressant effects of opioids, prompting caution in use of these drugs for treatment of OUD.

Financial Support: National Institute of Health grants DA049886 to L.F.B and DA011792 and DA043204 to J.K.R

In Vivo Monitoring of Tonic Serotonin Concentrations and Respiration Rate Following Fentanyl Infusion and Neuromodulation

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Drug Category: Opiates/Opioids
Topic: Neurobiology/Neuroscience
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research

Aim: Fentanyl is a synthetic opioid 50-100x more potent than morphine. Its rising prevalence in the U.S. is a major contributor to the ongoing drug epidemic and accounted for over 70,000 deaths in 2021. Fentanyl is thought to increase serotonin (5-HT) concentrations within the brain, making it a promising biomarker for substance use disorder (SUD) pathogenesis and therapy efficacy. Here, we present in vivo monitoring of tonic 5-HT concentrations with N-shaped multiple cyclic square wave voltammetry (N-MCSWV) following fentanyl administration and deep brain stimulation (DBS) of a potential therapeutic target for SUD.
Methods: A carbon fiber microelectrode was implanted into the nucleus accumbens core (NAcc) of anesthetized rats. A stimulating electrode was placed in the ventral tegmental area (VTA). Baseline tonic 5-HT concentrations were recorded with N-MCSWV. Deep brain stimulation (130Hz, 0.2ms pulse-width, 0.2mA) was then initiated followed by administration of fentanyl (i.v., 50□g/kg). The animal's respiration rate was recorded with an external monitor placed underneath the animal (RespiRat).
Results: Fentanyl increased 5-HT concentrations within the NAcc by 18.39 +/- 6.63% from baseline with a concurrent decline in respiration rate from 125.3 breaths/min before infusion to 82.7 breaths/min post-infusion. DBS of the VTA lowered tonic 5-HT concentrations post-fentanyl infusion by 31.02% (n = 1) from baseline and partially reversed the resultant respiratory depression after 15 minutes of continuous stimulation (45.8 to 85.1 breaths/min.).
Conclusions: Fentanyl administered intravenously increases tonic 5-HT concentration levels in the NAcc. DBS of the VTA decreases tonic 5-HT levels in the NAcc following infusion of fentanyl and reverses opioid-induced respiratory depression, a potentially fatal side-effect of opioid overdose. Future work will incorporate 5-HT monitoring and neuromodulation within opioid-addicted animal models.
Financial Support: This research was supported by the Uihlein Professorship Research Grant and NIH Awards T32GM145408-1, 5R01NS112176-04, 1R42NS125895-01A1, and 1R01NS129549-01.

Intranasal Versus Intravenous Naloxone in Pediatric Opioid Poisoning: A Pilot Randomized Clinical Trial

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Drug Category: Opiates/Opioids
Topic: Harm Reduction
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research

Aim: The worldwide opioid epidemic also affects children and adolescents, but treatment options in the pediatric population are much less explored. We aimed to evaluate nasal naloxone in opioid-poisoned pediatric patients by measuring the time from the treating physician's decision to administer the antidote to the return

of normal respiration. The hypothesis was that intranasal (IN) administration of naloxone is not clinically inferior to intravenous (IV) administration if the time it takes to place a secure intravenous line is considered.
Methods: In a hospital-based non-inferiority randomized pilot clinical trial, n=40 pediatric opioid-poisoned children were assigned in a 1:1 ratio to receive either IV (0.8mg/2ml) or IN (1.26mg/0.1ml) naloxone in addition to basic first aid. The time from physician's decision of antidote treatment to the return of normal respiration and/ or regaining consciousness was the outcome. Adverse events, need for additional naloxone, re-intoxication, parental, and staff satisfaction were also recorded.
Results: The median age of the participants were 24.5 months with 26 boys and 14 girls. Twenty-nine (72.5%) children had abnormal respiration, and 40 had reduced consciousness at the time of admission. After intervention, all cases in both groups responded to naloxone administration, while two cases (one in each group) required an additional IV dose. IV cannula insertion took a median of 35 seconds (IQR 25, 49). Decision to administer naloxone, IV cannulation plus response to naloxone was 68 seconds (IQR 50, 82) in the IV group and 23 seconds (IQR 20, 52) in the IN group.
Conclusions: The pilot study shows that IN naloxone is not clinically inferior to IV in terms of time to clinical response if the time effort for IV cannulation is considered.
Financial Support: Study funds were provided by Shahid Beheshti University of Medical Sciences. The study drug used in this trial was donated by the Norwegian University of Science and Technology (NTNU), Trondheim (Norway).

ORAL SESSION: CIRCUITS AND SUBSTRATES: MOLECULAR NEUROSCIENCE OF ADDICTION

Cellular Effects of Cannabinoids in Adolescent Cortex: A Translational Study in Mice and Humans

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Drug Category: Cannabis/Cannabinoids
Topic: Neurobiology/Neuroscience
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research
Aim: Growing evidence confirms an association between cannabinoid use and developmental changes to cortical thickness during adolescence, when experimentation with cannabis has been associated with cortical thinning in the frontal lobe. Considering that circuit maturation is a trans-species feature of cortical maturation, we assessed whether cannabinoid-induced transcriptomic changes to the cortex of adolescent mice revealed relevant processes underlying cortical thinning in human adolescents who experimented with cannabis.
Methods: We used unbiased single-cell transcriptomics to identify cells targeted by repeated administration of delta9-tetra-hydro-cannabinol (THC)(n=6) or the synthetic cannabinoid WIN 55,212-2 (WIN)(n-4) to adolescent (male) mice.
We then used MRI across 34 regions to examine differences in cortical thickness between human males who had experimented with cannabis before age 16 (n=140) or had not (n=327).

Finally, we identified the human homologues of the genes modified by THC or WIN in murine cortex that had a known and consistent inter-regional profile of expression in human cerebral cortex.

Results: In single cell transcriptomics in mice, THC modified the expression of 223 and WIN; 172 genes in murine frontal cortex. (Wilcoxon rank-sum test log2= LESS THAN 0.25, p= LESS THAN 0.05) THC preferentially targeted glial cells, WIN mainly affected pyramidal neurons. Both cannabinoids produced marked downregulation of respiratory subunits in mitochondrial complexes I-V, representing 31% of genes modified by both treatments.

65% (13/20) of the genes modified by THC and 58% (18/31) modified by WIN that were eligible for analysis of cortical distribution had an expression profile that spatially correlated with regional differences in cortical thickness in adolescents that had used cannabis (r= GREATER THAN +/-0.3, p= LESS THAN 0.05).

Virtual histology further revealed that cannabinoid-sensitive genes whose distribution correlated with cannabis-related changes in cortical thickness also co-distributed with cell-specific markers for pyramidal cells, astrocytes and microglia (p= LESS THAN 0.05).

Conclusions: We speculate that experimenting with cannabis during adolescence may influence cortical thickness via cellular processes that impact dendritic arborization of pyramidal neurons.
Financial Support: Canadian Institutes of Health Research (CIHR), Fonds d'Accélération des Collaborations en Santé (FACS)

Role of Altered Neural Circuits of Stress and Reward Regulation in Alcohol Use Disorder and Treatment-Related Recovery

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Drug Category: Alcohol
Topic: Neurobiology/Neuroscience, Stress
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research
Aim: Stress and trauma have adverse impacts on alcohol use disorder (AUD). Yet, underlying neurobiological mechanisms remain unclear. To clarify neural mechanisms of stress and AUD, the current study investigated neurobehavioral responses to stress and alcohol cues using functional magnetic resonance Imaging (fMRI).
Methods: Demographically-matched, 65 moderate drinkers (MD) and 53 AUD individuals (mean age=33; 52% female) completed an fMRI task involving the viewing of stress and alcohol cues. After the scan, AUD patients received an 8-week outpatient treatment using combined breathing-based stress reduction and cognitive behavioral methods. A subset of AUD patients (N=29) also completed a second fMRI session after treatment.
Results: AUD showed higher craving response to stress and alcohol-cue (ps LESS THAN 0.001). A threshold of $p<0.001$ with cluster correction at $\alpha=0.05$ was used for all fMRI results below. AUD displayed altered fMRI responses to stress and alcohol-cue in cortico-limbic-striatal regions including hypoactive ventromedial prefrontal cortex (vmPFC) but hyperactive limbic-striatal responses including amygdala, hippocampus, and striatum. AUD with a history of early trauma showed even more decreased VmPFC responses to stress than AUD with no early trauma. After 8-week treatment, AUD showed reduced craving ratings during stress and alcohol cues (ps LESS THAN .01). In addition, VmPFC responses were increased during stress and alcohol cues, while amygdala and insula responses were reduced. Particularly, VmPFC recovery during stress was associated with greater improvements in stress management ability after treatment ($p<.001$).
Conclusions: AUD displayed compromised neural circuits of stress and reward regulation, characterized by hypoactive VmPFC, but hyperactive limbic-striatal responses. After receiving integrated alcohol treatment combining stress management, AUD showed improved VmPFC function and greater ability to regulate stress. These findings highlight the importance of neural circuits of stress and reward regulation in AUD. Integrating stress reduction in alcohol treatment may help recover neural dysfunction and promote better treatment outcomes.
Financial Support: (Supported by grants: R01-AA026844; R01-AA13892). Yale Kavli Institute for Neuroscience

NPAS4-Expressing Ensemble in the Nucleus Accumbens Facilitates Drug-Related Behavior

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Drug Category: Other, Stimulants (cocaine) and Opioids (heroin)
Topic: Neurobiology/Neuroscience
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research
Aim: Expression of Neuronal PAS Domain Protein 4 (Npas4) is induced in a select ensemble of cells within the nucleus accumbens (NAc) following drug exposure. Our previous work has shown Gi-DREADD-mediated inhibition of this ensemble decreases cocaine conditioned place preference (CPP), the ensemble is composed primarily of medium spiny neurons (MSNs; ~75%), and NPAS4 itself regulates cell type-specific activation balance in the NAc following cocaine exposure. We hypothesize that non-MSN cells included in the ensemble are mostly GABAergic interneurons and inhibition of the ensemble during re-exposure to a drug-associated cue will decrease cue-reinstated drug-seeking behavior.
Methods: To define the Npas4+ ensemble, we conducted single nuclei RNA sequencing (snRNA-Seq) with NAc tissue collected from adult male and female wildtype C57BL/6J mice directly from the home cage or 15 minutes after cocaine conditioning (n = 4/group). To determine the role of this ensemble in drug self-administration, we are injecting AAV-DIO-GiDREADD-mCherry into the NAc of NPAS4-TRAP mice. Animals will undergo acquisition, extinction, and reinstatement phases of self-administration, with Npas4+ cells TRAPed during the first three days of acquisition and inhibited via Gi-DREADD during reinstatement.
Results: We find significant upregulation of Npas4 in Drd1, Drd2, and Grm8 positive MSNs (unpaired t-tests, $p<0.001$) after cocaine conditioning compared to naïve controls. We also observe that the cell type population distribution of all Npas4+ cells and of "highly" expressing Npas4+ cells (top 25%) resemble the neuronal distribution, suggesting non-biased recruitment of cells to the ensemble. Non-MSN Npas4+ cells are primarily Pnoc, Pvalb, Sst, or Th positive interneurons. Self-administration studies detailed above are currently ongoing.
Conclusions: The Npas4+ ensemble facilitates cue-reward associations, which often trigger a return to drug-seeking behavior after a period of abstinence. Understanding the molecular mechanisms by which this occurs may aid in identifying points for therapeutic intervention in substance use disorder.
Financial Support: T32 DA007288 (JLH), F31 DA048557 (BWH), R01 DA032708 (CWC), DA046373 (CWC)

Sex-Dependent Association of Fos-Expressing Neuronal Ensembles in the Nucleus Accumbens With Cocaine-Primed Seeking in Rats

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Drug Category: Stimulants
Topic: Neurobiology/Neuroscience
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research
Aim: Individuals with Cocaine Use Disorder experience high rates of relapse that contribute to increased morbidity and mortality. Evidence from rat models of relapse to cocaine use suggests that sparse groups of neurons (i.e., neuronal ensembles) in the nucleus accumbens (NAc) encode learned associations that drive cue-induced cocaine-seeking, a relapse-like behavior. However, the role of neuronal ensembles in drug-primed cocaine-seeking has not been explored. Additionally, the role of sex in neuronal ensemble activation associated with drug-primed cocaine-seeking is poorly understood. Since females reportedly exhibit greater cocaine-primed seeking than males, determining if neuronal ensemble activation drives this behavioral sex effect is essential.
Methods: To address these knowledge gaps, the present study investigated the role of sex on volitional cocaine-taking, cocaine-seeking following forced abstinence, and Fos-based neuronal ensemble activation in the rat NAc.
Results: Consistent with previous literature, females self-administered more infusions of cocaine and exhibited greater cocaine-primed seeking than males. Neuronal ensemble activation was observed, but contrary to our hypothesis, females and males did not differ in NAc Fos activation after cocaine-seeking. Furthermore, NAc Fos activation was significantly correlated with cocaine-seeking in males but not females.

Conclusions: These results suggest that, while necessary for cocaine-primed seeking behavior, NAc ensemble activation is insufficient to drive the observed behavioral sex-effects. Circulating sex hormones and sexually dimorphic reward circuitry are implicated in cocaine-seeking, and future investigations should be performed to examine their interaction with relevant ensemble populations.
Financial Support: T32-GM139807, R21-DA052657, R01-DA042057, GM118983

ORAL SUBMISSION: POUTINE THE TREATMENT WHERE IT COUNTS: BUPRENORPHINE INDUCTION METHODS

ED Use of Extended-Release 7-Day Injectable Buprenorphine for Minimal Opioid Withdrawal

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Drug Category: Opiates/Opioids
Topic: Treatment
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research
Aim: Emergency Department (ED) 7-day extended-release injectable buprenorphine (XR-BUP) for patients in minimal/mild withdrawal is feasible and safe
Methods: A single arm prospective study (N=100) using XR-BUP CAM2038 24mg (16mg daily equivalent) in 4, geographically diverse, EDs. Patients< 18 years with opioid use disorder (OUD) and Clinical Opiate Withdrawal Scale (COWS) score 0-7 were included if urine testing negative for methadone. Primary outcomes: number of patients with 1)< 5 increase in COWS within 4-hours; 2) transitioned to COWS< 13 within 4-hours; and 3) experienced precipitated withdrawal (PW) within 1-hour. Data from participants with an increase of< 5 COWS was reviewed and adjudicated for PW by two external experts . COWS were assessed q30 minutes up to 4 hours post injection. 7-day follow-up included engagement in addiction treatment, adverse events, and patient satisfaction.
Results: From 7/2020-5/2023, 635 patients were screened and 100 enrolled; 63 (COWS 4-7) and 37(COWS 0-3); 72% male, mean age of 36; 50% White, 35% Black and 12% Hispanic; and 70% fentanyl positive urine. Ten (10%) experienced< 5 increase in COWS scores and 7 transitioned to COWS< 13. Seven (7%) experienced PW, 5 (13.5%, 95%CI 4.54-28.77) at COWS 0-3 and 2 (3.2%, 95%CI 0.39-11.00) at COWS 4-7; 2 within 1-hour of injection. Injection mean pain score was 2.9 immediately; and 0.6 at 240 minutes. There was no erythema (96%) or swelling (97%) at 30 minutes, with 98% having neither at 240 minutes. At 7-day follow up, 73 (73%) were engaged in OUD treatment. There were 14 adverse events, 7 PW, 1 nausea and vomiting 1 temporary loss of smell and 5 hospitalizations (2 PW, 1 depression, 2 cellulitis).
Conclusions: XR-BUP in ED patients with minimal opioid withdrawal is feasible, safe, and well tolerated with COWS of 4-7 and may improve treatment adoption.
Financial Support: This research was supported by the National Institutes of Health through the NIH HEAL Initiatives under award numbers UG1DA015831 and UG1DA013035

Comparative Effectiveness of Low Dose Initiation Buprenorphine Protocols for People with Fentanyl Use Disorder: A Longitudinal Cohort Study

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Drug Category: Opiates/Opioids
Topic: Treatment
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research

Aim: Initiating buprenorphine for opioid use disorder (OUD) has proved challenging in the fentanyl era due to increased risk of precipitated withdrawal when using traditional starting doses of buprenorphine. Low dose initiation (LDI) protocols circumvent this issue by introducing gradually increasing small doses of buprenorphine over several days, with continued full agonist opioid use. However, studies of LDI are limited to case reports with none evaluating effectiveness in outpatient settings. We sought to conduct a study to evaluate clinical outcomes associated with LDI use.
Methods: We conducted a retrospective cohort study of individuals with OUD and self-reported daily fentanyl use who were prescribed and picked up either a 7-day or 4-day LDI protocol for buprenorphine initiation. Medical records were reviewed for patients who selected either a 7-day or 4-day buprenorphine LDI in shared decision-making with an addiction treatment clinician and picked up a blisterpack of medications to complete LDI initiation from a specialized pharmacy. Data was collected across two San Francisco safety-net substance use disorder treatment clinics from May 2021 to November 2022. The main outcomes were successful completion, defined as reported LDI completion at a follow-up visit and pick up of a refill prescription for buprenorphine maintenance, and buprenorphine retention at 28 days. We used generalized estimating equations (GEE) to estimate the odds of completion and buprenorphine retention at 28 days across LDI protocols, adjusting for age, gender, race/ethnicity, and housing.
Results: We included 126 patients; they were predominantly young (mean age 37 years, standard deviation 10 years), cisgender male (71%), and white (52%). The majority were marginally housed or unhoused (60%) and smoked fentanyl as the primary route of use (79%). There were 175 LDI attempts, including 103 (59%) 7-day and 72 (41%) 4-day LDI attempts. Less than a third (28%, n=29) of 7-day attempts were completed, with 19 (18%) resulting in retention at 28 days. Outcomes for 4-day attempts were 38% completion (n=72) and 21% retention at 28 days (n=15). In adjusted analysis comparing 4-day LDI attempts to 7-day LDI attempts, the adjusted odds ratio (aOR) for completion was 1.53 (Confidence Interval [CI] 0.76-3.07) and for retention at 28 days was 1.30 (CI 0.59-2.87).
Conclusions: To our knowledge, this is the first known study evaluating comparative effectiveness of LDI protocols to initiate buprenorphine among people using fentanyl. Despite offering LDI in a specialized setting with blisterpacks to support adherence, LDI completion and subsequent buprenorphine retention were low. Possible challenges to LDI completion in outpatient settings include complicated medication instructions, ongoing fentanyl use, and competing priorities such as unstable housing. There may not be meaningful differences in outcomes across LDI protocols, and clinicians should rely on shared decision making and patient preference when deciding LDI protocol selection.
Financial Support: Research reported in this publication was supported by the Agency for Healthcare Research and Quality under Award Number K12HS026383.

Buprenorphine Precipitated Withdrawal in Hospitalized Patients with Opioid Use Disorder: Incidence and Risk Factors from a Community with High Fentanyl Prevalence

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Drug Category: Opiates/Opioids
Topic: Treatment
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research

Aim: Buprenorphine precipitated withdrawal (PW) incidence and risk factors are unclear for opioid use disorder (OUD) with fentanyl use. We (1) estimated PW incidence and (2) tested the hypothesis that five a priori-defined risk factors (e.g., higher initial doses of buprenorphine, higher BMI, and higher urine fentanyl concentration) are associated with PW.
Methods: This was a retrospective cohort study of 226 humans of both sexes. We extracted electronic health record data for adults who started buprenorphine at three hospitals in Philadelphia, PA in 2020-2021. We included patients who received an initial dose of sublingual buprenorphine< =2mg after scoring< =8 on the Clinical Opiate Withdrawal Scale (COWS). We defined PW as an increase in COWS< =5 documented within four hours of the first dose of buprenorphine. We report PW incidence overall and for patients with fentanyl or norfentanyl on urine drug testing (UDT). Using logistic regression, we conducted bivariate and multivariable analyses of risk factors for PW.
Results: Our primary cohort comprised 226 traditional buprenorphine initiations (mean 38.6 years [SD 10.8]; 76 [33.6%] female). In this cohort, 26 (11.5%) had PW and no risk factors were associated with PW. In the pre-specified subgroup of individuals with fentanyl or norfentanyl on UDT, PW incidence was 20 of 123 cases (16.3%). In this subgroup, BMI< 30 (vs. BMI>25) was associated with PW in bivariate (OR 4.3 [95% CI 1.2-15.0], p=0.023) and multivariable (OR 5.4 [95% CI 1.3-23.2], p=0.023) analyses, and higher urine fentanyl concentration of 40-399 ng/mL (vs.>40 ng/mL) was associated with PW in bivariate (OR 6.2 [95% CI 1.3-29.2], p=0.021) and multivariable analyses (OR 8.6 [95% CI 1.4-53.6], p=0.021).
Conclusions: PW incidence with traditional buprenorphine initiation was low but higher than in prior studies. Higher BMI and higher urine fentanyl concentrations were associated with higher odds of PW, suggesting that future studies should prospectively assess if persistent opioid agonism from bioaccumulated fentanyl is responsible for PW.
Financial Support: NIDA R34DA057507

A Mechanistic Pharmacological Model to Predict and Inform Effective Buprenorphine Treatment Induction Strategies in the Era of Synthetic Opioids.

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Drug Category: Opiates/Opioids
Topic: Treatment
Abstract Detail: Other
Abstract Category: Original Research
Aim: Buprenorphine treatment induction has been associated with an increased risk of precipitated withdrawal (PW) in chronic fentanyl users diagnosed with opioid use disorder (OUD). Using mechanistic (quantitative system pharmacology) modeling, our objective was to explore factors that might be responsible for increased incidence of PW in chronic fentanyl users and to predict buprenorphine induction strategies that minimize PW.
Methods: We developed a mechanistic pharmacological model for buprenorphine and fentanyl that integrates opioid pharmacokinetics, mu-opioid receptor (MOR) binding kinetics, MOR tolerance mechanisms, and characterizes the relationship between MOR agonist activity and Clinical Opiate Withdrawal Scale (COWS) scores. The fentanyl pharmacokinetic model included an adipose tissue compartment to investigate the impact of delayed release of lipophilic fentanyl on PW in chronic fentanyl users. The model was calibrated using published data on respiratory depression measured after intravenous administration of fentanyl and buprenorphine, either alone or in combination. The relationship between opioid agonist activity and COWS scores was estimated by analyzing data from a planned interim analysis (N=93) of a clinical study of buprenorphine induction in patients with fentanyl-positive urine tests. We will update the model with final data (NCT04995029,< 700 enrolled subjects).
Results: The model successfully described changes in COWS scores in patients with and without PW. The percentage of PW predicted by the model was 22% (95% CI: 14-30%) vs. 28% in the observed dataset. The model suggests that mechanistically, the occurrence of PW is related to an abrupt decrease in MOR agonist activity when buprenorphine is initially administered.

Conclusions: We developed a mechanistic model characterizing the effects of fentanyl and buprenorphine on MORs, respiratory depression, and COWS scores. This model enables the design of improved buprenorphine induction protocols to reduce the risk of PW in fentanyl-exposed patients while providing adequate MOR agonist activity to motivate patient continuation in maintenance treatment.
Financial Support: Financial Support provided by Indivior Inc.

ORAL SESSION: IMPACT OF RECENT TRAUMA ON DRUG USE

Association of Recent Traumatic Brain Injury With Subsequent Nonfatal Overdose Among People who Use Drugs in Vancouver, British Columbia, 2018 – 2020

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Drug Category: Polydrug (i.e. concurrent use two or more drugs)
Topic: Comorbidities
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research
Aim: Traumatic brain injury (TBI) among people who use drugs may increase the risk of overdose via behavioral and neurocognitive mechanisms. The aim of this study was to determine the association between recent TBI and subsequent nonfatal overdose.
Methods: Data were drawn from two ongoing prospective cohort studies, the Vancouver Injection Drug Users Study (VIDUS) and AIDS Care Cohort to Evaluate exposure to Survival Services (ACCESS), between December 2018 and November 2020. The primary explanatory variable was lagged (in the preceding six-month cycle) TBI and the primary outcome variable was nonfatal overdose in the subsequent six months. Multivariable generalized estimating equations (GEE) models were fit with the following possible confounders determined a priori: age, gender, ethnicity, incarceration, homelessness, childhood physical or sexual abuse, mental illness, depression, anxiety, engagement in opioid agonist therapy, and daily alcohol, benzodiazepine, stimulant, opioid, polydrug, and marijuana use.
Results: We analyzed data from 2,355 total subject-visits, with 244 (10.4%) subject-visits reporting at least one TBI. The most common cause of TBI was a fall (145/244, 59.4%) and most individuals reported mild TBIs (141/222, 63.5%) as indicated by fewer than 30 minutes of loss of consciousness. Among those without recent TBI, overdose in the last six months was reported in 255/2111 (12.1%), while among those with recent TBI, risk of overdose in the last six months was nearly doubled at 58/244 (23.8%). In adjusted analyses, individuals who reported TBI in the preceding six-month cycle had significantly higher odds of subsequent nonfatal overdose compared to individuals without preceding TBI (aOR 1.79, 95% CI 1.23-2.61, p = 0.003).
Conclusions: In this longitudinal cohort analysis of people who use drugs in Vancouver, individuals who reported preceding TBI had significantly higher odds of subsequent nonfatal overdose. Further research on the interaction between TBI and overdose, including efforts to prevent recurrent TBI and overdose, are warranted.
Financial Support: The VIDUS and ACCESS cohorts were supported by the US National Institutes of Health (NIH) (U01DA038886, U01DA021525). Gabriela Reed's work was supported by the International Collaborative Addiction Medicine Research Fellowship (NIDA R25-DA037756) and the Research in Addiction Medicine Scholars Program (NIDA R25-DA033211).

Does Social Connectedness Moderate the Impact of Trauma on Drug Use?

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Drug Category: Alcohol

Topic: Treatment
Abstract Detail: Other
Abstract Category: Original Research
Aim: There is an extensive amount of literature that explores the relationship between trauma symptoms and problematic substance. However, there is insufficient knowledge about the impact social connection through self-help recovery groups has on this relationship. This study explores the relationship between trauma symptoms and drug use, with a focus on how social connectedness moderates this relationship.
Methods: Data were collected from 142 male and female adult participants starting treatment at the HEARTS (HIV Education, Awareness, Referral and Treatment for Substance Use Disorders) program via questionnaires in Government Performance and Results Act (GPRA) Client Outcome Measures for Discretionary Programs developed by Substance Abuse and Mental Health Services Administration (SAMHSA). Trauma symptoms were measured by the Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5). Alcohol use was measured by the Alcohol Use Disorders Identification Test (AUDIT). Social connectedness was measured by items in the GPRA with the attendance of voluntary self-help groups for recovery, religious/ faith-affiliated recovery groups, other recovery meetings, and interactions with family and/or friends supporting recovery ranging from score 0 to 4. The data were analyzed with Poisson regression and moderation analysis using PROCESS for SPSS 29.
Results: The results of the Poisson regression showed a significant effect of PCL scores on AUDIT scores (χ^2 (1) = 25.312, p> .001), meaning greater trauma symptoms were associated with more problematic alcohol use. In the moderation analysis, we explored whether social connectedness moderates the effect of trauma on alcohol use. Interestingly, contrary to previous literature, this effect was not moderated by social connectedness (b = - .012, SE = .048, p = .802).
Conclusions: Contrary to past literature, we did not find a moderating effect of social connectedness on trauma and alcohol use. The results can be explained by the way social connection was defined in the current study (e.g., attendance in recovery groups).
Financial Support: This research was supported by grant funding provided by the Substance Abuse and Mental Health Services Administration (Dr. Angela Heads, PD/PI) Project Number SAMHSA MAI-CSAT: TI080734 TCE-HIV. All procedures were in accordance to the ethical standards of the University of Texas Health Science Center at Houston and approved by the Internal Review Board.

Racial Differences in the Effects of Exposure to Violence on Binge Drinking

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Drug Category: Alcohol
Topic: Criminal Justice
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research
Aim: Exposure to violence (ETV) and binge drinking in adolescence are two interconnected major public health concerns with direct implications for the U.S. justice system. Justice-involved adolescents (JIA) have higher rates of ETV and binge drinking, and JIA from certain Black and Latinx communities often suffer harsher consequences. However, racial differences in these relationships among JIA have not yet been explored. The objectives of this secondary data analysis were to investigate if cumulative ETV has an exposure-response effect on binge drinking episodes among JIA and assess if the impact of victimization on binge drinking is exacerbated or mitigated for racial/ethnic minorities relative to White individuals.
Methods: The sample comprised 1,354 JIA (86.58% male) from waves one and two of the Pathways to Desistance Study. The sample was followed across seven years following an adjudication for a serious offense. Ordered logistic regression was used to assess the impact of cumulative ETV on the frequency of binge drinking in the prior six months stratified by race/ethnicity.
Results: Cumulative violent victimization was associated with increased odds of binge drinking frequency among Black JIA only, and witnessing violence was associated with increased odds of binge drinking frequency among Latinx JIA only. These results indicated significant differences between the magnitude of the effect of baseline direct victimization history for Black and Latinx participants, with the effect on binge

drinking being significantly stronger for Black participants (OR=1.438; p<.004). No other significant differences between racial groups were identified for either ETV variable.
Conclusions: Intervention efforts may benefit from integrating weathering and inoculation hypotheses to pinpoint the context and dosage by which stress may function as a protective factor or a risk factor. Intervention initiatives should be data-driven, and these findings are essential to inform culturally appropriate and trauma-informed interventions.
Financial Support: The research reported in this publication was supported by the National Institutes of Health under award numbers 1K01DA052679 (Dr. Micah E. Johnson, PI), R25DA050735 (Dr. Micah E. Johnson, PI, and Kimberly Johnson, co-PI), and R25DA059073 (Dr. Micah E. Johnson, MPI and contact PI). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the Florida Department of Juvenile Justice.

Reported Increase in Substance Use Following Exposure to Terrorism, and the Roles of Current Distress and Prior Mental Health Difficulties: Evidence From a Population Sample of Jewish Adults in Israel Following Hamas October 7 Attack

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Drug Category: Other, mass trauma and substance use
Topic: Comorbidities
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research
Aim: On October 7, Israel experienced an unprecedented terrorist attack. Studies have shown that an increase in substance use (ISU) is prevalent after such events. The current study examined reported ISU in Israel's adult Jewish population in the month following October 7. Demographic, psychological, and exposure characteristics were examined to explore which were associated with risk. Finally, the study evaluated whether psychological distress (PD) mediates the association between exposure and rISU and whether prior mental health difficulties (PMH) moderate it.
Methods: We conducted a quasi-representational web panel survey in November 2023 with 968 participants aged 18-70 (M= 41.5, SD = 14.6). The study included rISU, direct, indirect, and media exposure, PD, and PMH as measures. We employed a multiple logistic regression to investigate the association between study variables and rISU, Model 4 Process macro to examine PD's role in the association between exposure and rISU, and Model 7 to determine whether PMH moderated these effects.
Results: Direct, indirect, and increased media exposure increased rISU by OR of 4.56, 2.47, and 1.23, respectively. PD and PMH were also significantly associated with rISU (OR: 1.87, 2.67, respectively). PD was higher among those exposed indirectly or via media, partially mediating the association of exposure and rISU (direct and indirect effects for indirect and media exposure, respectively: B = .5166, p=.0034; B=.2078, .1133 LESS THAN CI LESS THAN -.3198; B = .1806, p=.0004; B=.1396, .0967 LESS THAN CI LESS THAN .1897). There was no evidence for such association for direct exposure (B=.0514, -.3333 LESS THAN CI LESS THAN .2408). Furthermore, there was no evidence that PMH moderated the association between indirect exposure or media exposure and PD (b = -.0076, p = .9573; b = .0085, p = .8110).
Conclusions: The study expands on previous studies on how mass terrorism affects PD and ISU in the general population in the weeks following the event and may be used to guide healthcare and preventative efforts.
Financial Support: None

ORAL SESSION: RISKY BUSINESS: IMPULSIVITY IN SUDS

Effects of Combined Ethanol and Nicotine Administration on Delay Discounting in Sprague-Dawley Rats

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Drug Category: Polydrug (i.e. concurrent use two or more drugs)
Topic: Behavioral Pharmacology
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research
Aim: AIM: Ethanol (EtOH) and nicotine (NIC) are among the most commonly used and co-used drugs in the world. Co-use often occurs in people who only consume the drugs acutely, often in a "bingeing and chipping" pattern. Given existing evidence that each drug on its own can affect impulsive choice in delay-discounting procedures, the purpose of the present experiments was to investigate effects of combined acute EtOH and NIC at a range of dose combinations on delay discounting in rats.
Methods: METHOD: Eight male Sprague-Dawley rats were trained on a two-lever delay-discounting procedure. In Experiment 1, EtOH alone in sweetened gelatin (0-3 g/kg; p.o.) was tested; in Experiment 2, NIC alone (0-1 mg/kg; s.c.) and combined EtOH and NIC were tested. In both experiments, repeated-measures ANOVAs were conducted to assess effects of drug dose and session block on choice for the larger reinforcer.
Results: RESULTS: Relative to vehicle, 2 g/kg EtOH ($p = .010$), 3 g/kg EtOH ($p = .022$), 0.3 mg/kg NIC ($p = .042$), and 1 mg/kg NIC ($p = .027$) reduced choice for the larger reinforcer (i.e., increased impulsive choice) when administered individually, relative to vehicle. In general, combinations of the two drugs reduced choice for the larger reinforcer relative to vehicle and to each drug alone.
Conclusions: CONCLUSIONS: In a rat model, particular dose combinations of EtOH and NIC increased impulsive choice relative to either drug alone. These findings highlight complex pharmacological and behavioral interactions between EtOH and NIC and suggest that NIC administered after EtOH may have deleterious effects on impulsivity by compounding EtOH-induced increases in impulsive choice.
Financial Support: This study was supported by a dissertation award from the West Virginia University Department of Psychology and an Innovative Student Research Grant from the Society for the Advancement of Behavior Analysis.

Sensation Seeking, Impulsivity, and Nicotine Dependence among Adolescents and Young Adults who Vape Nicotine and Cannabis

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Drug Category: Other, Nicotine and Cannabis
Topic: Tolerance/Dependence
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research
Aim: Our aim is to identify individual factors associated with greater likelihood of vaping cannabis among adolescents and young adults (AYAs) who vape nicotine. We hypothesized that adolescents and young adults (AYAs) who vape nicotine are more likely to also vape cannabis if they experience greater sensation seeking, impulsivity, and nicotine dependence, and lower perceived control over quitting nicotine.
Methods: AYAs reporting past-30-day e-cigarette use were recruited via Qualtrics Online Sample (N=1,018) to complete an anonymous survey (ages 14-29; 55.0% female, 69.6% White, 16.3% Black, 19.4% Hispanic). We assessed for past-30-day nicotine and cannabis vaping; sensation seeking (3-items); impulsivity and self-control (8-item Barratt Impulsiveness Scale-Brief); reasons for vaping (10-items); nicotine dependence (4-items); and perceived control (1 item: "I could stop using e-cigarettes if I wanted to," from 1=strongly disagree to 5=strongly agree). We used logistic regression, controlling for age, gender, race/ethnicity, and frequency of e-cigarette use (range 0-30 days), to examine for differences in likelihood of past-30-day cannabis vaping depending on impulsivity, sensation seeking, reasons for vaping, nicotine dependence, and perceived control.
Results: AYAs who vape nicotine were more likely to have vaped cannabis in the past 30 days if they reported vaping to "relax/relieve tension" (OR=1.51, 95% CI= 1.09-2.10, p=0.02) or "feel good/get high" (OR=1.79, 95% CI= 1.28-2.49, p<.001); higher sensation seeking (OR=1.59, 95% CI= 1.34-1.88, p<.001); higher nicotine dependence (OR=1.22, 95% CI= 1.06-1.41, p<.01); and greater perceived control over e-cigarette use (OR=1.25, 95% CI= 1.09-1.42, p=.001).

Conclusions: Results indicate potential individual risk factors (e.g., sensation seeking) and reasons for vaping among AYAs who vape cannabis and nicotine (compared to nicotine only). Results indicate greater nicotine dependence among AYAs who vape both substances, but also greater perceived self-control over e-cigarette use. These findings may inform efforts to reduce dual nicotine and cannabis vaping among AYAs.
Financial Support: R01DA049878; T32 DA019426-18; U54DA036151

Impulsivity as a Moderator for the Relationship Between Anxiety, Depression and Alcohol Intake of Hazardous Drinkers

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Drug Category: Alcohol
Topic: Behavior
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research
Aim: Clinical research has consistently identified a relationship between Mood Disorders, Impulsivity and Alcohol Use Disorder. We aimed to explore whether impulsivity moderated the relationship between alcohol use and mood symptoms in a non-clinical sample, testing the hypothesis that individuals exhibiting greater impulsivity are more likely to self-medicate with alcohol when experiencing negative affect.
Methods: Participants (N = 937, Mage = 22.1) completed an online battery of questionnaires and cognitive measures including the Alcohol Use Disorders Identification Test, Generalised Anxiety Disorder Scale, Brief Patient Health Questionnaire Mood Scale, Monetary Choice Questionnaire, and a Stop Signal Task. We employed multiple hierarchical regression analyses to investigate the relative contributions of each predictor variable (anxiety symptoms, depressive symptoms, and impulsivity) in explaining variance on the outcome variable, alcohol use. Moderation analyses were also employed to assess whether impulsivity moderates the relationship between anxiety symptoms, depressive symptoms, and alcohol use.
Results: Hierarchical regression found a significant predictive effect of depressive symptoms on alcohol use behaviour. The analyses did not find a significant effect of anxiety symptoms or impulsivity on alcohol use behaviour. Moderation analyses found that impulsivity, measured by delay discounting and inhibitory control, did not moderate the relationships between alcohol use and anxiety and depressive symptoms.
Conclusions: The current study suggests that in non-clinical populations, the relationship between alcohol use and anxiety, alcohol use and depression, and the moderating role of impulsivity is nuanced. The results highlight the importance of understanding the role of alcohol consumption in subclinical psychopathology.
Financial Support: None

Clinical Translation of the HR/LR Model of SUD Propensity

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Drug Category: Stimulants
Topic: Behavioral Pharmacology
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research
Aim: Identifying vulnerability markers for substance use disorders is key to clarifying pathways to addiction and developing effective long-term treatments. It is also crucial to identifying at-risk individuals and directing prevention and intervention efforts. Trait novelty seeking has been associated with drug use initiation and transition to compulsive use. In preclinical studies, locomotor activity in a novel environment is proposed as a behavioral analogue for trait novelty-seeking; rats with the greatest activity (High Responders, HR) acquire psychostimulant self-administration faster and consume more drug compared to rats with the least activity (Low Responders, LR). However, the relationship between activity in a novel environment, trait novelty-seeking, and sensitivity to drug reward is unverified in humans. In this study, we sought to replicate the preclinical findings in humans.

Methods: Healthy men and women completed an exploration test in a novel environment (monitored by closed circuit cameras) and standardized personality questionnaires. They then completed testing sessions with methamphetamine (0, 20mg, randomized order; double-blind administration) and reported mood and drug effects before, and at repeated times after drug administration. Activity scores in the novel environment were rank ordered, and individuals with scores in the top and bottom thirds (respectively HR and LR, N=30 each) were compared on methamphetamine subjective effects and personality traits.
Results: In comparison to LR, HR reported significantly greater positive subjective effects of methamphetamine (ps LESS THAN 0.05), scored significantly higher on trait impulsivity ($p<0.05$) but not novelty-seeking, and comprised a greater proportion of men.
Conclusions: Our findings support the preclinical HR/LR model of SUD propensity in men and show that that motor response to novel environments is associated with trait impulsivity but not novelty seeking. The results are among the first to show relationships between laboratory measures of behavioral and cognitive measures of impulsivity and suggest future directions for sex/gender differences research in SUD.
Financial Support: This research was supported by NIH grant DA033488 (EC).

ORAL SESSION: STRETCHING THE HELIX: TRANSLATIONAL GENETICS

Genomic Assessment of the Prefrontal Cortex in Differential Responsivity of Sucrose Preference and Fentanyl Escalation in Sprague-Dawley Rats

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Drug Category: Opiates/Opioids
Topic: Behavior, Behavioral Genetics
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research
Aim: The “loss of control” phenomenon seen in opioid use disorder (OUD), known as escalation of intake, is well-established in preclinical rodent models. Antecedent behavioral characteristics, such as valuation of hedonic reinforcers prior to drug use, may impact the trajectory of fentanyl intake over time. Moreover, phenotyping escalation of fentanyl intake may reveal the underlying genetic markers associated with OUD.
Methods: Male and female Sprague-Dawley rats (n=58) were trained in a sucrose reinforcement task using a progressive ratio schedule. Individual differences in responsivity to sucrose were hypothesized to predict escalation of fentanyl intake. Rats underwent daily 1h acquisition sessions for i.v. fentanyl self-administration (2.5 µg/kg; FR1) for 7 days, then 21 6h escalation sessions. Approximately 18h after the last self-administration session, tissue from prefrontal cortex (PFC) was collected for RNA sequencing and qPCR. Permutation testing was used to assess gene expression using original and post-hoc statistical models involving behavior during the three weeks.
Results: Sucrose breakpoints did not predict fentanyl infusions across 1h sessions but did predict fentanyl infusions across 6h sessions; however, the association with sucrose breakpoints was with the initial daily levels rather than the temporal changes over the three weeks. During the acquisition phase, female rats displayed greater intake compared to males ($F(1, 63)=7.7$, $p=0.007$). However, when given extended access to fentanyl, there was no significant sex difference in fentanyl intake ($F(1, 56)=1.8$, $p=0.19$). Our permutation analysis did not identify associations between behavior and gene expression.
Conclusions: Valuation of the hedonic reinforcer sucrose predicted initial daily levels of fentanyl infusions in 6h sessions but not temporal changes. Bulk-sequencing did not identify differentially expressed genes in connection to behavior. Future investigations with greater statistical power will continue to seek clues into genomic markers of OUD.
Financial Support: Supported by: NIH R01 DA053070

Beyond Euphoria: Transcriptomic Investigation in the rat Brain Under the Administration of Fentanyl Combined With Xylazine

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Drug Category: Polydrug (i.e. concurrent use two or more drugs)
Topic: Genetics/Proteomics/Metabolomics
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research

Aim: The ongoing opioid epidemic in the United States has escalated with the emergence of 'tranq dope', a perilous combination of opioids, particularly fentanyl, and the veterinary tranquilizer xylazine. The combination of fentanyl and xylazine not only prolongs the euphoric effects of fentanyl but also inflicts severe physical consequences, including bruises, infections, and necrotic wounds, often resulting in limb amputations. This lethal mixture, associated with a surge in overdoses and fatalities, poses unique challenges in treatment due to the ineffectiveness of naloxone against xylazine and evidence suggesting naloxone is less effective against fentanyl in the presence of xylazine. The study aims to investigate the transcriptional effects of 'tranq dope' and its constituents on the nucleus accumbens (NAc), and how they vary between sexes.
Methods: We conducted an isoform-resolved transcriptomics study of the NAc of male and female Sprague Dawley rats that received twice daily intraperitoneal injections of fentanyl (45 mg/kg), xylazine (2.5 mg/kg), fentanyl+xylazine, or saline for 14 days (n=4/sex/treatment).
Results: We identify treatment- and sex-specific differences in gene and isoform level expression patterns in the NAc, a crucial region associated with the reward circuitry and of substantial interest in addiction studies. Downstream bioinformatics identified associated biological pathways and putative molecular mechanisms of the differential expression.
Conclusions: Considering prior evidence demonstrating sex-specific differences in opioid administration, either alone or in combination with other substances, our sex-specific differences are unsurprising and further support the need for studies that disentangle the effect of sex on the neurobiological mechanisms of addiction. These studies holds the potential to significantly contribute to the limited understanding of the effects of fentanyl combined with xylazine and provide rigorous justification for future investigations that seek to further understand the molecular mechanisms of opioid-polysubstance abuse
Financial Support: This work was supported by the University of Pennsylvania (B.C.R.).

Cocaine-Induced Gene Expression in rat Lines Selected for Altered Drug Self-Administration

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Drug Category: Stimulants
Topic: Genetics/Proteomics/Metabolomics
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research

Aim: The LS and HS rat strains have been selectively bred for Low and High intravenous Self-administration of opioids and cocaine. To better understand the specific genetic loci that underlie alterations in reward behavior, we compared cocaine-induced changes in RNA expression in the nucleus accumbens.
Methods: Sixteen rats (8 LS and 8 HS) male rats received injections of vehicle or cocaine (3.2 mg/kg), with brain dissection three hours later. RNA was extracted from the nucleus accumbens and sequenced to a depth of 25 million paired-end reads over 100 bases on an Illumina NovaSeq 6000 flow cell. Statistical significance was determined by t test.
Results: Cocaine modified gene expression in 303 genes, with 255 genes altered significantly in HS but not LS animals. Of these, 15 genes exhibited greater than four-fold changes in expression. The two genes with the greatest differences were heat shock protein family B (small) member 7 and centromere protein U, both involved in cellular differentiation and tumor suppression. The third most differentially expressed gene, fibroblast growth factor 19, plays a role in neural development and bile acid synthesis. Major functional categories of altered genes included cellular signaling (12.7), transcription (8.8), cell cycle control (7.7), RNA processing (7.3), cellular localization (6.8), and receptor function (6.4). More than 12 percent of altered genes have no currently recognized function.

Conclusions: These findings implicate altered expression at genetic loci involved in cellular signaling and differentiation, transcription, and receptor function; which may underlie altered drug reward in the LS and HS rat strains.
Financial Support: Supported by Merit Review Award Number I01 BX004748 from the Department of Veterans Affairs Biomedical Laboratory R and D Service.

Multi-Omic Understanding of the Genetics of Opioid Addiction: A Review

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[1]*RTI International,* [2]*The Jackson Laboratory,* [3]*The Whitehead Institute,* [4]*Oak Ridge National Laboratory,* [5]*Johns Hopkins Bloomberg School of Public Health,* [6]*University of California San Diego,* [7]*Geisinger College of Health Sciences*

Drug Category: Opiates/Opioids
Topic: Genetics/Proteomics/Metabolomics
Abstract Detail: Other
Abstract Category: Literature Review
Aim: Opioid misuse, addiction, and associated overdose deaths remain global public health crises. Estimates are that more than 60 million people around the world currently misuse opioids, over 21 million people suffer from opioid use disorder and 125,000 people died of an opioid overdose in 2019. Despite this tremendous need, pharmacological treatment options are limited in their number, use, and effectiveness. Fundamental leaps forward in our understanding of the biology driving opioid addiction are needed to guide development of more effective MAT. This review focuses on the omics-identified biological features associated with opioid addiction.
Results (Optional): Overall, recent genome-wide association studies (GWAS) are beginning to reach sufficient size to identify robust genetic associations that are consistent across studies and related phenotypes. Top GWAS signals include variants in OPRM1, FURIN, and across the gene cluster SCAI, PPP6C, RABEPK. In parallel, there are an increasing number of omics studies of postmortem human brain, examining a variety of biological features (e.g., DNA methylation, histone modification, RNA and protein expression) across different brain regions. These studies are beginning to identify broad gene dysregulation associated with overdose death among opioid misusers – both genetically and exposure driven dysregulation. Drawn together by meta-analysis and multi-omic systems biology, and informed by model organism studies, key biological pathways enriched for opioid addiction associated genes are emerging. Dysregulated features common across omics types and studies include specific receptors (e.g., GABA, GPCR, and RTKs) linked to signaling pathways (e.g., ERK/MAPK, Orexin, Trk) associated with synaptic plasticity and neuronal signaling.
Conclusions: Continuing to leverage the agnostic discovery power of omics and placing it within the context of functional neurobiology will push us forward to much needed, field-changing breakthroughs and identification of actionable targets for drug development and new treatments for this devastating brain disease.
Financial Support: NIDA P50 DA054071

ORAL SESSION: NURTURING FUTURES: SUPPORTING AND TREATING PREGNANT INDIVIDUALS WITH SUBSTANCE USE DISORDER

County-Level Neonatal Opioid Withdrawal Syndrome Rates, Rurality, and Buprenorphine Access During Pregnancy in the American Midwest: A Secret Shopper Study

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Drug Category: Opiates/Opioids
Topic: Prenatal/Perinatal
Abstract Detail: Clinical - Epidemiology

Abstract Category: Original Research
Aim: There is a common perception that a higher burden of neonatal opioid withdrawal syndrome (NOWS) is concentrated in rural and suburban areas in the U.S. with low buprenorphine capacity. Yet, recent data has suggested that the demographics of the overdose crisis are shifting, with people residing in urban areas experiencing surging rates of overdose. We computed county-level buprenorphine access rates for pregnant people and examined the associations between NOWS rates and 1) buprenorphine access and 2) rurality in the state of Missouri, which has been strongly afflicted by the overdose crisis.
Methods: Up to 3 phone calls were made to all buprenorphine prescribers in Missouri in 2019 through early 2020 to determine if clinicians were accepting new pregnant patients. County-level buprenorphine capacity was defined as the number of clinicians (across all specialties) accepting pregnant people divided by the number of births. Multivariable negative binomial regression models estimated associations between buprenorphine capacity, rurality (rural vs urban vs suburban), and county-level NOWS rates, controlling for potential confounders such as poverty, unemployment, and physician shortages Analyses were stratified using tertiles of county-level overdose rates (top, middle, and lowest 1/3 of overdose rates).
Results: Of 115 Missouri counties, 81 (70%) had no buprenorphine capacity, 17 (15%) were low-capacity (LESS THAN 0.5-clinicians/1,000 births), and 17 (15%) were high-capacity (GREATER THAN 0.5/1,000 births). The mean NOWS rate was 6.5/1,000 births. In counties with both the highest and lowest opioid overdose rates, higher buprenorphine capacity did not correspond to decreases in NOWS rates (incidence rate ratio [IRR]=1.23 [95% confidence interval [CI]=0.65-2.32] and IRR=1.57[1.21-2.03] respectively). Rurality did not correspond to greater NOWS burden in both counties with highest and lowest opioid overdose rates.
Conclusions: The vast majority of counties in Missouri have no capacity for buprenorphine prescribing during pregnancy. Contrary to common perception, rurality and lower buprenorphine capacity did not significantly predict elevated rates of NOWS.
Financial Support: K12 DA041449

Prenatal Drug Use Criminalization and Health System avoidance: Evidence from Births in Alabama, South Carolina, and Tennessee, 1989-2019

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Drug Category: Opiates/Opioids
Topic: Prenatal/Perinatal
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research
Aim: We tested whether adoption of pregnancy criminalization policies was associated with changes in the county-level prevalence of pregnancy-related health services utilization: prenatal care, and facility-based delivery, from 1989 to 2019.
Methods: Data were from restricted National Vital Statistics System birth certificate files, aggregated to the county-year-level. Primary outcomes included the prevalence of any prenatal care versus no care, and the prevalence of facility-based delivery, including hospital, birth center or clinic, versus residence or other settings. Secondary outcomes included prevalence of prenatal care timeliness and prevalence of prenatal care adequacy. We generated estimates using county fixed effects models that also controlled for secular trends affecting all counties, adoption of co-occurring policies and time-varying factors influencing criminalization and pregnancy care outcomes, for example state political ideology. Sensitivity analyses tested a variety of different specifications including refinement of the exposure definition, inclusion of additional confounders, and models specified with an alternative functional form.
Results: The adoption of policies explicitly authorizing criminal prosecution of prenatal drug use was associated with 4396.29 fewer births per 100,000 receiving any prenatal care (95% Confidence Interval [CI]: -6176.07, -2616.51) over the observation period. The adoption of criminalization policies was further associated with 1847.99 fewer facility-based deliveries (CI: -3688.29, -7.69), however estimates were imprecise across some sensitivity analyses. We did not observe clear changes in the prevalence of births with

timely (-1328.43; CI: -3108.21, 451.36) or adequate (- 792.21; CI: -2571.99, 987.58) prenatal care following criminalization, but some models suggested reductions in timeliness.
Conclusions: Findings support the premise that policies explicitly criminalizing pregnant drug use reduce pregnant people's utilization of prenatal care and potentially facility-based delivery. To the extent that pregnant people with drug use disorders are among those most likely to benefit from these services, criminalization therefore exacerbates the population-level negative consequences of prenatal drug use.
Financial Support: EB is supported by the Substance Abuse Epidemiology Training Program (SAETP) at Columbia University, funded by the National Institute on Drug Abuse (DA031099).

Exploration of Substance Use Recurrence by Psychiatric Comorbidities within a Sample of Pregnant Patients in Treatment for Opioid Use Disorder

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Drug Category: Opiates/Opioids
Topic: Prenatal/Perinatal
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research
Aim: Mental health conditions are the leading underlying cause of perinatal death, namely overdose related to opioid use disorder (OUD) followed by suicide. Untreated psychiatric conditions and OUD often lead to worse outcomes than either disorder alone, yet how these conditions intersect during pregnancy in relation to treatment outcomes has not been well elucidated. This study compares substance use recurrence by psychiatric comorbidity in sample of pregnant people receiving medication for OUD (MOUD).
Methods: This secondary analysis examines data from N=27 pregnant people with OUD participating in a randomized clinical trial assessing a technology-based educational intervention. Inclusion criteria were:>34 weeks gestation, ≥18 years old, not planning adoption, receiving MOUD, and engaged in integrated OUD and prenatal care (recruitment site) for>10 weeks. At baseline, participants provided information on psychiatric treatment and past month substance use (timeline follow-back) via interview. Chi Square test compared substance use recurrence by comorbid psychiatric diagnosis as abstracted from the medical record [anxiety-related disorder (n=4), mood disorder (n=9), and both anxiety-related and mood disorder (n=14)].
Results: Participants were predominately white (67.7%) and Black (25.9%), 30.2 (SD=4.5) years old and 23.2 (SD=6.8) weeks pregnant. Over half had experienced an overdose (55.6%). Rate of substance use recurrence was significantly higher among participants with a comorbid mood disorder (77.8%) than those with an anxiety-related disorder (25%), or both (28.6%) ($p<0.05$). The most frequently used substance among mood disorders was cocaine (33.3%), anxiety disorders sedatives (100%), and both opioids (37.5%). Most participants were engaged in psychotherapy (74.1%). Mood disorder participants had the lowest rates of psychiatric medication use (44% vs. anxiety 50% vs. both 64.3%).
Conclusions: Pregnant people in OUD treatment with a comorbid psychiatric condition, namely mood disorder, are likely at increased risk of substance use recurrence. Optimizing screening for and provision of treatment for perinatal mood disorders is essential in this population.
Financial Support: This work was supported by the Virginia Commonwealth University CCTR Endowment Fund, the Jeanann Gray Dunlap Foundation, the National Institute of Drug Abuse (K23DA053507; T32DA007027) and partially by the National Center for Advancing Translational Sciences (UM1TR004360).

Persistent Racial Inequities in Methadone Dose among Pregnant Women with Opioid Use Disorder

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Drug Category: Opiates/Opioids
Topic: Racial/Ethnic Differences

Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research
Aim: Black pregnant women with opioid use disorder (OUD) receive significantly lower doses of methadone than White women at delivery, suggesting undertreatment of OUD. It is not known when this inequity emerges, e.g., during protocolized initiation of methadone based on Clinical Opioid Withdrawal Scale scores or during outpatient maintenance. The present study was designed to further evaluate racial inequities in methadone for OUD among pregnant women and determine when inequity emerges to find points to intervene.
Methods: Data were extracted from medical charts for pregnant women who received inpatient methadone initiation at our urban academic medical center between January 2020 and June 2022. Extracted data included demographic and health characteristics, substance use variables, OUD treatment variables, and delivery outcomes. Race was dichotomized as Black or White as few reported other races. Chi-square, t-tests and multiple regressions evaluated associations between variables and dose at end of inpatient methadone initiation and at delivery. P> 0.05 was considered statistically significant.
Results: 170 pregnant women received inpatient methadone initiation (139 White, 31 Black) and 94 had a live birth at the same hospital (81 White, 13 Black). At initiation, Black women had higher BMI (p=.046), were more likely to use prescription opioids (p<.001), and less likely to use tobacco (p=.033). In multiple regression, BMI (p=.036) and race (p=.044) remained significantly associated with methadone dose at the end of methadone initiation with Black women receiving 32mg less methadone. In unadjusted comparisons, Black women had lower methadone doses at delivery than White women (p=.034), but this was not significant in multiple regression (p=.051).
Conclusions: Racial inequities in methadone dose emerged during protocolized initiation and trended toward persisting through delivery. This suggests that initiation protocols, tools, or their application may be driving racial inequities. Anti-racism/anti-discrimination approaches are needed to ensure Black pregnant women with OUD receive equitable treatment.
Financial Support: None

ORAL SESSION: BEYOND X AND Y: SEX DIFFERENCES IN ADDICTION

Sex Differences in Risky Decision-Making Brain Activation Within Frontotemporal Circuitry and Cerebellum for Youth At-Risk for Substance Use

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Drug Category: Other, Polydrug Substance Use Disorder Risk
Topic: Sex/Gender Differences, Sex/Gender Differences and Imaging
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research
Aim: To investigate the association between sex and risky decision-making brain activation in adolescents with externalizing psychopathology (EXT). We hypothesize that EXT and healthy control (HC)-females will have greater activation in relevant frontoparietal areas compared to males during risky decisions and when reacting to loss.
Methods: This cross-sectional study included 179 substance-naïve 11-12-year-olds, grouped as EXT-males (EXT-M=85) and females (EXT-F=42) who have high SUD risk and HC-males (HC-M=35) and females (HC-F=17). Youth performed an fMRI-compatible Balloon Analogue Risk Task (a risky decision-making task), producing fMRI-BOLD data for choice (Choose-Inflate) and outcome regressors (Outcome-Explode). A whole brain analysis identified regions of interest with significantly different contrast activation between groups. Linear regression modeling stratified by contrast was adjusted by pubertal stage and parental education. Significance level was set at α =05.
Results: During Choose-Inflate, HC-M (β=0.64,p<.001), EXT-F (β=0.70,p<.001), and EXT-M (β=0.65,p<.001) had greater activation in the right middle temporal gyrus (MTG) than HC-F. Lower activation was found during Outcome-Explode in the left angular gyrus (AG) for EXT-F (β=-0.96,p<.001) and EXT-M (β=-0.71,p=.008), and left anterior superior frontal gyrus (SFG) for HC-M (β=-0.53,p=.03) and EXT-M (β=-

0.57,p=.01), when compared to HC-F. During Outcome-Explode, HC-M (β=0.42,p=.02) and EXT-M (β=0.47,p=.005) had greater activation in the left cerebellar lobule VIII than HC-F.
Conclusions: Atypical risky decision-making in addiction and risk models occurs when making risky choices (Choose-Inflate) and reacting to loss (Outcome-Explode). Our findings suggest that regions related to reaction in risky choice and decision-making (MTG, cerebellum), and attention to/learning from loss and loss aversion (AG, SFG) differ between the reference group (HC-F) and the EXT groups representing higher decision-making activation reactivity and lower loss aversion in at-risk youth, particularly EXT-M. These sex differences in at-risk youth's decision-making are translationally relevant for understanding risk and generating sex-specific interventions for SUDs which could target decision-making processes.
Financial Support: This study is supported by NIDA-grant: 5R01DA039764.

Sex Differences in Contextual Cocaine Seeking Behavior are Driven by Noradrenergic Signaling to the Dorsal Hippocampus

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Drug Category: Stimulants
Topic: Neurobiology/Neuroscience
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research
Aim: Individuals suffering from substance use disorders are susceptible to relapse when presented with contextual cues, suggesting that contextual memories associated with drugs of abuse impede abstinence success. Women may have greater difficulty maintaining abstinence; an effect recapitulated in rodent models. β-adrenergic receptors (β-ARs) have a long-standing historical implication in driving processes associated with contextual drug memories, and therefore may play a role in context-induced cravings. However, sex differences in the adrenergic system driving drug memories remain unknown.
Methods: Herein, we tested the sex differences in the roles of dorsal hippocampus (dHPC) β-ARs in non-operant and operant cocaine memories using cocaine conditioned place preference (Pavlovian; CPP) and cocaine-seeking persistence during extinction from self-administration (operant; CSP) in male and female adult Sprague Dawley rats (n=6-8/group). We administered β-AR antagonists (Betaxolol (β1) and/or ICI 118,551 (β2)) to the dHPC prior to retrieval in both CPP and CSP. We then investigated sex differences in the projections of locus coeruleus norepinephrine (LC-NE) neurons to the dHPC during CSP using DREADDs.
Results: Intra-dHPC administration of both β1+β2 antagonists attenuated Pavlovian conditioning in both sexes. Administration of either antagonist attenuated CPP in males only. In females however, intra-dHPC β1 antagonists impaired recall, whereas β2 impaired retention, of CPP expression. Notably, the involvement of β-ARs differed under operant conditions, as CSP was attenuated by β-AR antagonists in females only. Similarly, inhibition of LC-NE signaling to the dHPC using DREADDs attenuated operant cocaine-seeking in females only.
Conclusions: There are significant sex differences in the role of dorsal hippocampus β-ARs in the encoding and expression of both Pavlovian and operant cocaine memories. Furthermore, these effects may be driven by sex differences in adrenergic tone between the locus coeruleus and dorsal hippocampus. Thus, the substantial sex differences in the retrieval and retention of cocaine memories may be driven in part by adrenergic signaling.
Financial Support: R00 DA045758

Sex Differences in Cannabis Use Disorder Among a Cohort of Cannabis Consumers: Preliminary Results From the Herbal Heart Study

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Drug Category: Cannabis/Cannabinoids
Topic: Substance Use Disorder
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research
Aim: Cannabis use disorder (CUD), which according to DSM-5 is the combination of cannabis abuse and dependence, is a behavioral disorder from problematic patterns of cannabis use that has become a major public health concern, impacting 3 out of 10 cannabis consumers. Prior studies have reported a higher prevalence of cannabis consumption among men compared to women. With the rising prevalence of cannabis use among young adults (18-35), our objective was to explore sex disparities in CUD prevalence.
Methods: Data are from the ongoing Herbal Heart Study (N=150) of 18-to-35-year-olds in South Florida; baseline data from cannabis consumers (n=76) were analyzed. Sex at birth was self-reported. CUD was assessed using the Cannabis Use Disorder Identification Test - Revised (CUDIT-R) and categorized as either non-hazardous cannabis use (CUDIT-R>8), hazardous cannabis use (CUDIT-R between 8-11), or possible CUD (CUDIT-R< 12). Mean CUDIT-R scores and prevalence of CUD were compared between male and female via t-tests and Chi-squared/Fisher's Exact Test, respectively.
Results: The mean age was 25.0 years (SD=4.3), 57.9% female, 55.3% Hispanic, and 73.3% were employed. The mean CUDIT-R score for the sample was 14.1 (SD=5.7). There was a significant difference in mean CUDIT-R score between males and females (15.6; SD=4.5 and 13.1; SD=6.3, respectively, $p=0.04$). The majority of both males (83.9%) and females (60.0%) presented with possible CUD ($p=0.01$) while 24.4% of females and none of the males had non-hazardous cannabis use ($p<0.01$).
Conclusions: Findings suggest that more research is warranted to investigate the factors associated with sex differences in cannabis use disorders among young adults, in order to improve intervention strategies and provide evidence-based cannabis literacy for informed usage of cannabis.
Financial Support: NHLBI R01HL153467 (PI: Denise Vidot); NIMHHD T37MD008647 (PI: Johis Ortega)

Differential Effects in Gaba Receptor Regulation Between Sexes and its Role in Cocaine Use Disorder

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Drug Category: Stimulants
Topic: Sex/Gender Differences
Abstract Detail: Preclinical - In Vitro
Abstract Category: Original Research
Aim: Cocaine use disorder (CUD) is characterized by cocaine-induced alterations in dopamine release in the nucleus accumbens (NAc). Critically, sex differences in dopamine release both in basal and drug-induced processes play a causal role in sex-specific behaviors associated with CUD – where females show enhanced vulnerability. While work has focused on sex differences in the anatomy of dopamine neurons and relative dopamine levels, an important characteristic of dopamine release from axon terminals is that it is rapidly modulated by local regulatory mechanisms independent of somatic activity. GABA released from local microcircuitry in the NAc has been shown to play a critical role in regulating dopamine release at the terminals through ionotropic GABA-A and Gi-coupled GABA-B receptors and has also been implicated in cocaine-induced processes. Here we define basal sex differences in dopamine release regulation via GABA in the NAc and show how this is dysregulated by chronic cocaine exposure.
Methods: To dissociate dopamine terminal regulation from somatic regulation, we utilize ex vivo fast scan cyclic voltammetry and optogenetics in striatal brain slices of naïve and cocaine-exposed mice. Dopamine release was evoked from terminals via electrical and optogenetic stimulation, and GABA receptor modulation of this signal was determined via bath application of picrotoxin (GABA-A antagonist), muscimol (GABA-A agonist), saclofen (GABA-B antagonist), and baclofen (GABA-B agonist) to slices. This was done in the absence and presence of nicotinic acetylcholine receptor antagonist DHBE to determine if GABA receptor modulation was mediated through cholinergic interneurons. For statistical analysis, unpaired t-tests were conducted when comparing two groups. In all other experiments, we utilized two-way ANOVA analysis, along with Holm-Sidak's multiple comparisons tests.

Results: GABA-A and GABA-B receptor agonists decreased dopamine release in the striatum similarly in males and females. However, sex differences were observed in antagonizing GABA receptors following both electrical and optogenetic stimulation. Picrotoxin, GABA-A antagonist, increased dopamine release to a greater extent in females compared to males [sex x drug interaction, $F(4, 42) = 4.289$, $p = 0.0053$], and this effect remained in the presence of DHBE. Saclofen, GABA-B antagonist, increased dopamine release to a greater extent in males compared to females [sex x drug interaction, $F(3, 21) = 11.92$, $p > 0.0001$]; however, this sex difference was only observed in the absence of DHBE. Lastly, GABA mediated inhibition of dopamine release was blunted following cocaine exposure in both males and females.
Conclusions: These data highlight differential effects in GABA receptor regulation of dopamine release between sexes. First, there is enhanced GABA-B-mediated inhibition in males that is modulated through cholinergic interneurons. Secondly, GABA-A mediated inhibition was enhanced in females and this effect was independent of nicotinic receptors, suggesting this mechanism is directly at the dopamine terminals. Finally, these mechanisms undergo cocaine-induced plasticity highlighting its potential role in CUD. The results of these studies will contribute to the understanding of how sex fits into the comprehensive framework for dopamine release regulation and how dysregulation of these processes influences the trajectory of CUD in both males and females.
Financial Support: Funds from the National Institute of Drug Abuse (NIDA) F31-DA056221supported this work.

ORAL SESSION: CHASING THE HIGH: EXPLORING THE NEUROBIOLOGY OF COCAINE USE DISORDER

Structural Brain Changes Associated With Cognitive Behavioral Therapy in Cocaine Use Disorder Treatment

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Drug Category: Stimulants
Topic: Treatment
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research
Aim: While studies have investigated changes in brain structure and function associated with recovery from cocaine use disorder (CUD), few have identified changes associated with specific CUD treatments and their active ingredients, which could inform treatment development and optimization. This study aimed to identify changes in brain structure as a function of pharmacological and psychosocial addiction treatment.
Methods: In this longitudinal study, T1-weighted magnetic resonance imaging scans were acquired from 41 methadone-maintained individuals with CUD (15 women) at the beginning of and after 12 weeks of outpatient CUD treatment. As part of a larger randomized controlled trial, these individuals were additionally randomly assigned to receive (or not) computer-based training for cognitive-behavioral therapy (CBT4CBT), and galantamine (or placebo). Measures of self-reported cocaine use and CBT4CBT engagement (i.e., number of modules completed) and knowledge (a CBT quiz at the start and end of treatment) were collected.
Results: Irrespective of treatment condition, whole-brain voxel-based morphometry analyses revealed a significant decrease in caudate body, cerebellum, and middle temporal gyrus gray-matter volume (GMV) at post-treatment relative to pre-treatment (pFDR LESS THAN 0.05). Subsequent region-of-interest analyses found that greater reductions in caudate and cerebellar GMV were associated with higher relative and absolute levels of cocaine use during treatment, respectively. Participants who completed more CBT4CBT modules had greater reductions in middle temporal gyrus GMV, which were associated with greater increases in knowledge of CBT.
Conclusions: These results extend previous findings regarding changes in caudate and cerebellar GMV as a function of cocaine use and provide the first evidence of changes in brain structure as a function of CBT for addiction. These data suggest a novel potential mechanism underlying how CBT4CBT and CBT more broadly may exert therapeutic effects on substance-use-related behaviors through brain regions implicated in semantic knowledge and communication processing.

Financial Support: This work was supported by P50DA09241. LYM was and is supported by NIDA-funded trainings grants T32DA019426 and T32DA022975, respectively.

The Subjective Value of Cocaine Cues in the Rostral Prefrontal Cortex Guides Decisions in People with Cocaine Use Disorder

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Drug Category: Stimulants
Topic: Imaging
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research

Aim: Drug-associated cues promote continued drug use, but the neurobehavioral mechanisms of this phenomenon are not well understood. Decision theory research has shown that choices between options are based on relative reward values. A dynamic choice task, neuroimaging (fMRI) and reinforcement learning (RL) modeling were used to test the hypothesis that cocaine cues add subjective value to choice options in people with cocaine use disorder (CUD).
Methods: Participants (N=17, 8f) meeting criteria for CUD performed two versions of a probabilistic choice task (cocaine vs. neutral cue; neutral vs. neutral cue). Selecting a cue option could result in a "win" ($0.25), but the options' reinforcement probabilities differed and reversed unpredictably. The RL model included an exchange rate parameter used to calculate subjective value of the cocaine-cued option relative to the alternative in monetary terms. Paired t-tests compared choice behavior and outcomes between cocaine- and neutral-cued tasks. General linear models corrected for multiple comparisons isolated neural activity associated with subjective value in each task. Bivariate correlations examined relationships between neural activity, subjective value and choice behavior.
Results: Participants made significantly more (MEAN±SEM) cocaine-cued choices than neutral-cued choices (180.47±5.7 vs. 148.29±3.1; $t(16)=4.9, p<0.001$) despite no difference in money earned. The relative subjective value of the cocaine-cued option in the cocaine-cued task was significantly greater than the corresponding neutral task option ($0.35±0.8 vs. $0.25±0.2; $t(16)=3.1, p=0.003$). Activity in the rostral prefrontal cortex (rPFC) was positively associated with subjective value of the cocaine-cued option ($kE=91$, $pFWE\text{-}corr=0.01$) and correlated with cocaine-cued choices ($r=.63, p=0.007$); significant correlations were not observed for the neutral task.
Conclusions: This study demonstrates that cocaine cues add subjective value to choice options, which could contribute to cocaine use decisions. The associated neural activity was isolated in the rPFC, which could be considered as a target for the development of neuromoduation interventions for CUD treatment.
Financial Support: R01DA045023, K01DA043652, T32DA035200, UL1TR001998

Neurobehavioral Differences in Value-Based Decision-Making Between People with Cocaine Use Disorder and Controls

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Drug Category: Stimulants
Topic: Imaging, behavior, reinforcement learning
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research

Aim: Decision theory research has shown that choices between options are based on relative reward values. Value is determined by objective and subjective attributes that change over time, requiring ongoing tracking of option values to guide decisions. A dynamic probabilistic choice task, neuroimaging (fMRI) and

reinforcement learning-based computational modeling were used to assess value-based decision-making in people with cocaine use disorder (CocUD) and matched controls (n=17/group). We hypothesized group differences in "rich" option choices, reinforcement learning modeling parameters and model-based brain activity.
Methods: In this task, two options were signaled by distinct cues and choosing either could have resulted in a "win" ($0.25), but the reinforcement probabilities (6:1/1:6, probabilities summed to 0.3) of the options differed and reversed unpredictably. Behavioral data were analyzed using t-tests (choices), AIC scores (model comparisons) and Mann-Whitney tests (model parameters). For neuroimaging data, average beta scores from a first-level general linear model representing value-modulated activity during choice deliberation/selection were extracted from regions of interest and a) compared between groups using t-tests and b) correlated with model parameters using Pearson's tests.
Results: The CocUD group made fewer rich choices compared to controls ($t_{32}=2.31$, $p=0.03$). A reinforcement learning model containing learning, inverse temperature and perseveration parameters provided the best fit of choice data (all subjects). The CocUD group had lower inverse temperature estimates ($U=46$, $p=0.0004$), demonstrating a reduced likelihood of selecting an option based on value. The CocUD group also had lower value-modulated activity in the lateral orbital frontal cortex (lOFC; $t_{32}=2.18$, $p=0.04$, corrected). Inverse temperature estimates were positively correlated with value-modulated lOFC activity (all subjects; $r_{32}=0.41$, $p=0.016$).
Conclusions: This study detected differences in value-based decision-making between CocUD and control groups and identified an underlying reinforcement learning-based neurobehavioral mechanism. These value processing differences could help explain the maladaptive drug use decisions that characterize cocaine use disorder.
Financial Support: R01DA045023, K01DA043652, T32DA035200 and UL1TR001998

Pregnenolone Effects on Cocaine Use in Individuals with Cocaine Use Disorder

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Drug Category: Stimulants
Topic: Treatment
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research
Aim: Chronic cocaine use is associated with decreases in neuroactive steroid levels. These adaptations may contribute to continued cocaine use and high relapse risk in individuals with cocaine use disorder (CUD). Thus, this pilot study assessed chronic treatment with 2 supraphysiologic doses of the neuroactive steroid precursor pregnenolone (PREG, 300 mg/day; 500 mg/day) to boost endogenous neuroactive steroid levels and assess its impact on cocaine use outcomes in an 8-week trial in men and women with CUD.
Methods: Fifty-three treatment-seeking individuals with CUD were randomly assigned to receive either placebo (PLA; n=18; 12M/6F), 300mg PREG/day (n=20; 15M/5F) or 500mg PREG/day (n=15; 11M/4F) for 8 weeks, along with outpatient weekly relapse prevention treatment. Plasma was collected at weeks 2, 5 and 7 to assess circulating pregnenolone levels. Participant cocaine use was measured via daily smartphone assessments and intent to treat analyses were conducted using linear mixed effects models.
Results: Plasma pregnenolone levels were higher in the 300mg ($p<0.001$) and 500mg ($p<0.001$) PREG groups compared to PLA. Participant trial completion rates were 94% for PLA, 85% for 300mg and 87% for 500mg PREG groups. There were no significant baseline group differences in cocaine use, and the groups did not differ in age or gender ratio. There was a significant main effect of treatment group ($p=0.03$) on the amount of cocaine use while controlling for age and gender. The 300mg PREG group reported significantly lower amounts of cocaine use compared to the 500mg PREG group ($p=0.01$) and also marginally significantly lower amount of cocaine use compared to PLA ($p=0.06$).
Conclusions: These pilot findings suggest that supraphysiologic neuroactive steroid PREG doses may improve cocaine use outcomes in treatment seeking individuals with CUD. Findings support further assessment and development of PREG in the treatment of CUD.
Financial Support: K01DA046561 (Milivojevic), R01AA026514 (Sinha).

ORAL SESSION: THE POWER OF PREDICTION: MACHINE LEARNING APPLICATIONS IN SUD RESEARCH

Identification of a Neural Network Predicting Thrill-Seeking in College Students: Sex-Specific Associations With Alcohol and Substance Use

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Drug Category: Other, Alcohol and other substances (e.g., marijuana, cocaine, opioids, psychedelics)
Topic: Neurobiology/Neuroscience
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research

Aim: Impulsivity is a multifaceted transdiagnostic construct linked to addictions. Yet assessments and conceptualizations of impulsivity often do not converge, and sex differences have been reported across various impulsivity domains, rendering it difficult to target effectively in addiction treatment. The current study aims to identify neural features underlying different facets of impulsivity and to explore their relationship to alcohol and substance use across women and men.
Methods: We utilized a whole-brain machine learning strategy, connectome-based predictive modelling (CPM), to investigate brain networks linked to four composite impulsivity-related domains previously identified by principal components analysis in the NIAAA-funded Brain and Alcohol Research in College Students (BARCS) study data: (1) impulsive action; (2) approach/appetitive motivation; (3) impulsivity/compulsivity; and (4) thrill-seeking/fearlessness (TS). CPM (5-fold cross-validation, 100 repeats, and permutation testing) was applied to monetary incentive delay task (MIDT) fMRI data from 287 undergraduate students and neural features identified in successful models were examined in relation to alcohol and drug use across women and men.
Results: The CPM model predicting TS was significant ($r = 0.24$, $p = .001$). Results indicated that higher TS was associated with stronger connectivity between default mode, motor/sensory, and cerebellar networks, and reduced connectivity between the medial frontal, frontoparietal, default mode, and motor/sensory networks. TS network strength differed significantly between men and women ($t(285) = 7.98$, $p > .001$) and was associated with alcohol use, binge drinking, cannabis, cocaine, crystal meth, heroin, opium, inhalants, ecstasy, PCP, and GHB use (ps> .05) in men only. Conversely, TS network strength was associated with pain medicine use ($p > .05$) in women only.
Conclusions: The identification of a neural network predicting thrill-seeking/fearlessness in young adults has potential implications for how impulsive behaviors may be targeted. Future work should consider sex differences and whether targeted interventions (e.g., neuromodulation) may help individuals seeking treatment for addictive behaviors motivated by thrill-seeking.
Financial Support: NIDA T32 Neuroimaging Sciences Training in Substance Abuse Program (DA022975), and K08DA051667

Development and Validation of Prediction Models for Perioperative Opioid Requirements: Integrating Machine-Learning Approach with Conventional Regression Method

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Drug Category: Opiates/Opioids
Topic: Health Services
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research

Aim: Excessive perioperative opioid prescribing has been detrimental to public health, contributing to the rise in the prevalence of opioid use disorder. Since 2016, rigorous regulations of opioid prescribing have reduced

over-prescription but have also led to opioid phobia. The 2022 CDC guideline promotes person-centered decisions on pain management by relaxing restrictions on opioid prescriptions. This study aims to develop and validate prediction models for perioperative opioid requirements to aid clinical decision-making.
Methods: Patients aged 18-64 years undergoing one of 12 commonly performed procedures (e.g., laparoscopic cholecystectomy) between 2015-Q4 and 2018 at a single institution were analyzed. Perioperative opioid requirements (none/low, medium, high) were determined based on the patient's self-reported pain scores and opioid prescription/administration from 30 days before to 2 weeks after surgery. Patient's clinical and procedure-related factors were collected as potential predictors. Random forest, the Least Absolute Shrinkage and Selection Operator (LASSO), and multinomial logistic regression were used to develop prediction models.
Results: We included 2733 surgical patients in the training dataset and 1081 in the testing dataset. All prediction models demonstrated moderate discrimination in the testing dataset, with C-statistics ranging from 0.646 to 0.674. The null hypotheses of perfect calibration intercepts and calibration slopes were rejected. In analyses restricted to patients undergoing laparoscopic cholecystectomy, model discrimination remained similar while model calibration improved greatly. The revised LASSO model had the highest accuracy (67.1%) in classifying future cases correctly into opioid requirements groups, with the highest sensitivity (84.9%) in the high requirement group and the highest specificity (99.2%) in the medium requirement group. Features in the final model included opioid/NSAIDs/antidepressants use before surgery, emergency surgery, anesthesia type, and surgical indication for cholelithiasis/cholecystitis.
Conclusions: The surgery-specific model outperformed the universal model including various surgery types. The incorporation of a machine-learning approach and subject-matter knowledge produces the best predictions of opioid requirements in the cholecystectomy cohort.
Financial Support: None

Predicting Subjective Response to Drug Cues Based on Objective Neuroimaging: An fMRI Machine Learning Study

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Drug Category: Other, Methamphetamine
Topic: Artificial Intelligence
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research
Aim: Craving is a central aspect of substance use disorder (SUD), traditionally assessed through subjective self-report measures that are inherently introspective and susceptible to contextual influences. In response to the growing need for more objective assessments, a neuromarker is proposed by Leonie Koban, Tor Wager and Hedy Kober in 2023 using fMRI drug cue reactivity and machine learning tools which distinguishes drug users (cigarettes, alcohol and cocaine) and non-users and also predicts the level of craving. Following this path, we employed a series of machine learning tools to establish objective neural biomarkers using fMRI drug cue reactivity data based on the people with methamphetamine use disorder.
Methods: Block-designed fMRI data, characterized by alternating blocks of neutral and methamphetamine-related images, were obtained from a sample of 68 participants diagnosed with methamphetamine use disorders. Concurrently, Likert-based cue-induced cravings were assessed at the end of each block. Employing Principal Component Analysis (PCA), feature selection algorithms and regression-based machine learning techniques, we established a robust predictive model for craving intensity based on consistent patterns of brain activity.
Results: Two methodologies were employed using 5-fold cross-validation with 20% holdout (untouched testing data) for predicting craving levels based on fMRI data. The first involved two stages, utilizing Principal Component Analysis (PCA) followed by linear regression, resulting in a Root Mean Squared Error (RMSE) of 0.93 ± 0.01. The second method employed Analysis of Variance (ANOVA) followed by Lasso regression, yielding an RMSE of 1.05 ± 0.04. For the classification task involving all levels of craving, the first algorithm achieved a classification accuracy of 0.36 ± 0.01 and Cohen's Kappa of 0.41 ± 0.01. The second algorithm achieved a classification accuracy of 0.34 ± 0.02 and Cohen's Kappa of 0.33 ± 0.04. Further distinguishing the highest and lowest craving levels, the first algorithm achieved an accuracy of 0.77 ± 0.03 and an AUC of

0.85 ± 0.013. The second algorithm achieved an accuracy of 0.73 ± 0.03 and an AUC of 0.78 ± 0.041. After comparative analysis, PCA followed by linear regression emerged as the superior choice with a statistically significant difference. The selected model exhibited p-value> 0.0003 using permutation test, and an accuracy of 0.838 and an AUC of 0.86 when tested on holdout data. These findings indicate that voxels in the inferior frontal gyrus, amygdala, precentral gyrus, and inferior parietal lobule carried the highest predictive weight for anticipating the subjective response to drug cues.
Conclusions: We developed a computational pipeline for robustly predicting the craving intensities using brain activations. This research contributes to advancing our understanding of craving in SUD and offers potential avenues for using objective measures/biomarkers in the development of targeted interventions and treatment strategies.
Financial Support: This project is funded by T32 Training Program in Genetic and Neurobehavioral Mechanisms of Addiction. Grant #: T32DA050560.

Predicting Alcohol Use Patterns From Diverse Longitudinal Datasets Using Novel Machine Learning Techniques

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Drug Category: Alcohol
Topic: Artificial Intelligence
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research
Aim: Develop machine learning algorithms to analyze heterogeneous longitudinal alcohol data and apply tools to uncover drinking patterns and predictors across diverse alcohol use disorder datasets.
Methods: Algorithms included generalized linear, additive, partial linear, Gaussian process, regression tree, and Bayesian additive regression tree models. These were adapted to account for within-person and between-person heterogeneity over time in alcohol use data. The toolkit was applied to analyze several alcohol use datasets: naturalistic drinking cohorts, clinical trials of alcohol use disorder treatments, and data from an mHealth app for reducing drinking. Participant characteristics, psychological measures, neuroimaging data, and up to 720 days of daily drinking data served as candidate predictors of drinking patterns.
Results: The toolkit successfully uncovers distinct drinking trajectories and predictors in each application dataset. The predictive performance of the tailored machine learning models is good, demonstrating the value of adapting algorithms for the intricacies of longitudinal alcohol data. For example, by adopting random effects to capture the subject-specific longitudinal trajectories in the ABQDrinQ cohort study, the algorithm correctly classified 84% of heavy drinking days, substantially outperforming traditional models without random effects (73% correct).
Conclusions: This machine learning toolkit demonstrates the importance of tailoring tools for the complexities of alcohol use disorder data compared to one-off analyses. Next steps include refining the algorithms, streamlining workflows, and improving individualized prediction dashboards based on user feedback. These advances will further enhance the toolkit's value in unraveling drinking patterns and their predictors to provide services that empower alcohol researchers.
Financial Support: NIH/NIAAA Phase II SBIR Contract 75N94023R00001

ORAL SESSION: DELVING INTO DISPARITIES: EXAMINING THE DRUG USE CONTINUUM AMONG VULNERABLE POPULATIONS AND RACIAL/ETHNIC MINORITIZED COMMUNITIES

Barriers and Facilitators for Engaging and Retaining Black Persons in Medications for Opioid Use Disorder (MOUD)

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Drug Category: Opiates/Opioids
Topic: Racial/Ethnic Differences
Abstract Detail: Other
Abstract Category: Original Research
Aim: Black persons have higher overdose death rates than Whites but are less likely to receive MOUD. Co-developed with a Community Advisory Board, this study (CTN-0088) aimed to identify barriers and facilitators to MOUD in predominantly Black communities in Washington, DC most affected by these disparities.
Methods: Interview guides included open-ended questions about the respondent's community, impact of substance use in the community; views about persons with opioid use disorder (OUD) and OUD treatments; and recommendations for addressing OUD. Participants in interviews or focus groups included persons with lived experience (N=28), family or friends (N=17), community leaders (N=31), and healthcare workers (N=57). Interviews were audio recorded and transcribed verbatim. Codebooks were developed using a rapid iterative process to identify themes and subthemes and then used to code all transcripts. The research team met weekly to discuss the coding and to organize and refine the themes.
Results: Across interviewee participant categories, five main themes were prominent: 1) stigma about persons with substance use disorders; 2) misunderstanding and negative views about MOUD (especially methadone programs, seen as eyesore in the community); 3) beliefs that the only successful treatments are long-term residential or abstinence-based; 4) beliefs that nothing can be done to get someone to stop using; and 5) peers and trusted community members are critical for fostering change. Many participants expressed skepticism about the motivations for the policy shift from criminalizing to using medications to treat addiction and noted the failure to address root causes. Persons receiving MOUD and some healthcare providers expressed support for MOUD and interest in advocating for MOUD.
Conclusions: Negative views about MOUD with methadone or buprenorphine are prevalent and deeply rooted, including among many healthcare workers. Countering these views is critical for increasing MOUD utilization and requires a multi-pronged, community-centered approach, including advocacy by knowledgeable peers, community leaders, and healthcare workers.
Financial Support: Supported by NIDA CTN-0088 and NIH HEAL initiative (UG1DA013034)

Drug Overdose Deaths Among Women 1999-2021 in the United States: Differences by Race/Ethnicity and age

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Drug Category: Polydrug (i.e. concurrent use two or more drugs)
Topic: Epidemiology
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research
Aim: The present study examines trends in U.S. drug overdose deaths among women by race/ethnicity and age group from 1999-2021.
Methods: We use data from the Centers for Disease Control and Prevention's Wide-Ranging Online Data for Epidemiologic Research (CDC WONDER) Multiple Causes of Death files using ICD-10 codes X40–X44, X60–X64, X85, and Y10–Y14 to identify overall drug overdose deaths, and T40.5 for cocaine-related deaths, T40.0-T40.4, T40.6 for opioid-related deaths, T42.4 for benzodiazepines, and T43.6 to identify psychostimulants. Race/ethnicity was defined as Non-Hispanic Black, White, American Indian/Alaska Native (AI/AN), Asian, and Hispanic. We calculated overdose death rates per 100,000 women for all drug overdose deaths and for specific substances (opioids, cocaine, benzodiazepines, methamphetamines) attributed deaths each year, stratified by race/ethnicity.
Results: From 1999-2021, drug overdose deaths among all women in the United States increased by 480%. Specifically, overdose deaths rose 750% for Non-Hispanic AI/AN women, 490% for Non-Hispanic Black women, 450% for Non-Hispanic White women, 325% for Hispanic women, and 150% for Non-Hispanic

Asian or Pacific Islander women. Women aged 35-44 (300% increase) and 45-54 (400% increase) saw the largest increases in overall drug overdose deaths during the study period. Cocaine-related deaths were more prevalent among Non-Hispanic Black women, opioid and methamphetamine-related deaths were more prevalent among Non-Hispanic AI/AN women, and benzodiazepine-related deaths were more prevalent among Non-Hispanic White women.
Conclusions: Increases in drug overdose deaths were noted in all races/ethnicities and age groups, with deaths continuing to accelerate in 2021. Our findings call for interventions expanding access to MOUD, naloxone, fentanyl test strips, and contingency management while accounting for gendered roles and vulnerabilities that impact women who use drugs.
Financial Support: K01DA051715 (PI: Jones)

Racial Disparities in Naloxone Access and Opioid Overdose Knowledge among Rural People who Use Drugs

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Drug Category: Opiates/Opioids
Topic: Racial/Ethnic Differences
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research
Aim: Opioid overdose response efforts have increased access to naloxone and knowledge of prevention strategies; however, Black people who use drugs (PWUD) experience increased overdose mortality risk. Due to underrepresentation of Black PWUD in rural substance use research, little is known about racial disparities in naloxone and overdose knowledge.
Methods: From August 2022-June 2023, we enrolled participants in Illinois' 16 southernmost counties who were 15 years of age or older and used opioids or stimulants within the past 30-days. Strategies to facilitate enrollment of Black PWUD included stakeholder engagement, supporting a Black peer champion to bridge study staff and the community, and venue-based recruitment. We report demographics, drug use, and conduct bivariate analysis to compare overdose experiences and knowledge, measured by the Brief Opioid Overdose Knowledge (BOOK) scale, stratifying by race.
Results: We enrolled 146 PWUD (M=45.8 years, SD 11.5); 56.2% were White and 37.7% Black. 7.5% used only opioids, 62.3% only stimulants, and 26.7% co-use of opioid and stimulants. More White and Other race reported previously accessing harm reduction services compared with Black participants (17.5% v. 23.1% v. 3.9%, p=0.03), receiving naloxone (40.0% v. 53.9% v. 21.6%, p=0.03), and currently possessed naloxone (36.3% v. 38.5% v. 14.3%, p=0.02). No statistically significant differences were reported in lifetime overdoses or ever witnessing another individual' overdose. Total BOOK scores were lowest among Black (M=7.1, SD 3.1) compared with White PWUD (M=8.4, SD 1.4) and Other race (M=8.6, SD 1.4) PWUD (p=0.01), indicating lower opioid and overdose knowledge.
Conclusions: Rural Black PWUD experience decreased naloxone access, opioid overdose knowledge, and harm reduction engagement compared with rural White peers. These disparities in overdose prevention efforts highlight the need for culturally tailored implementation strategies in rural areas as the fourth wave of the overdose crisis evolves.
Financial Support: Supported by NIDA 3UH3DA044829-05S1, 5UH3DA044829

School Suspensions Disproportionately Impact Already Vulnerable Youth: Evidence Supporting a Move Away From Exclusionary Discipline in Schools

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Drug Category: Polydrug (i.e. concurrent use two or more drugs)

Topic: Disparities
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research
Aim: Schools have historically relied on exclusionary punishment (e.g., suspension) to address violations to school policy (e.g., substance use). Because suspensions are ineffective deterrents that likely have a detrimental impact on both learning and sense of inclusion in the school environment, we sought to describe characteristics of students most likely to be suspended to inform development of alternative approaches.
Methods: In Fall 2022, 14,298 students from 60 Massachusetts' middle and high schools completed the MGH Substance Use and Risk Factor (SURF) survey of demographic factors, school engagement, and mental health functioning. A multi-level logistic regression with a school-varying intercept identified factors associated with past-year suspension.
Results: 487 (3.5%) students reported prior year suspension, with 25% of suspensions due to substance use. Factors associated with any suspension, in descending order of effect size, included poor academic performance (change in absolute risk [ΔAR]=6.1-18.9%), frequent cannabis, alcohol, or nicotine use (ΔAR=4.7-13.2%), past-year suicide attempt (ΔAR=3.4%), minoritized race (ΔAR=1.1-3.4%), current IEP (ΔAR=2.6%), psychotic experiences (ΔAR=2.1%), Hispanic ethnicity (ΔAR=1.5%), and male gender (ΔAR=1.1) (p's<0.04). An analysis of suspensions specifically for substance use identified the above factors and gender diverse identity (ΔAR=0.4%) and severe symptoms of depression/anxiety (ΔAR=0.2%) (p's>0.004). Those suspended for substance use were nearly 7-fold and 1.6-fold more likely to have a past-year suicide attempt compared to those not suspended and suspended for non- substance related infractions, respectively (no suspension: 2.6%; suspension not related to substance use: 7.7%; substance-related suspension: 19.7%; p's<0.001).
Conclusions: Suspensions disproportionately impact vulnerable youth with minoritized sociocultural identities and who are at-risk for academic disengagement, psychiatric and substance use disorders, and suicide. Implementing alternatives to suspension could reduce academic performance gaps, improve school connectedness, and address mental health factors that contribute to recidivism and are potentiated by disconnection inherent to exclusionary discipline.
Financial Support: Funds for this study are provided by the Massachusetts Department of Public Health, Office of Youth and Young Adult Services' federal award by the Substance Abuse and Mental Health Services Administration (INTF2400H78500224455; PI: Schuster), as well as the Patient Centered Outcomes Research Institute (AU-2022C1-26355; PI: Schuster).

ORAL SESSION: THE THRILL IS GONE: CHEMICAL DISRUPTION OF DRUG SEEKING AND TAKING

Effect of Chronic Delivery of the MOR/NOP Agonists AT-201 and AT-200 and the NOP Antagonist J-113397 on Heroin Relapse in a rat Model of Opioid Maintenance

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Drug Category: Opiates/Opioids
Topic: Treatment
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research
Aim: The opioid crisis persists despite availability of effective opioid agonist maintenance treatments (methadone and buprenorphine); this merits a need to advance novel medications for the treatment of opioid use and relapse. We recently modeled maintenance treatment in rats and found that chronic delivery of buprenorphine and the mu opioid receptor (MOR) partial agonist TRV130 decreases relapse to oxycodone seeking and taking. We also found that chronic delivery of the buprenorphine analog BU08028 had both beneficial and detrimental sex-dependent effects on different triggers of heroin relapse. Here, we tested the effect of mixed MOR/nociception receptor (NOP) agonists AT-201 and AT-200 and the NOP antagonist J-113397 on our heroin relapse-related measures.

Methods: We trained male and female rats to self-administer heroin (6-h/d, 14-d) in context A and then implanted osmotic minipumps containing AT-201 (0, 3.8, or 12 mg/kg/d), AT-200 (0, 2.6, or 6 mg/kg/d), or J-113397 (0, 12.6, or 40 mg/kg/d). We then tested the effect of chronic delivery of these compounds on (1) incubation of heroin seeking in a non-drug context B, (2) extinction responding reinforced by heroin-associated discrete cues in context B, (3) reinstatement of heroin seeking induced by reexposure to context A, and (4) reacquisition of heroin self-administration in context A.
Results: Chronic delivery of AT-201 or AT-200 did not decrease any of the heroin relapse measures and AT-201 unexpectedly increased reacquisition of heroin self-administration selectively in female rats. Results for J-112297 are pending.
Conclusions: Results suggest that mixed MOR/NOP agonists and NOP antagonists would not be effective opioid maintenance treatments in humans.
Financial Support: IRP/NIDA/NIH

A Quantitative Model of a Substitution Therapy Using Cocaine Self-Administration Behavior in Rats

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Drug Category: Stimulants
Topic: Behavioral Pharmacology
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research
Aim: A pharmacological theory of cocaine self-administration behavior states that cocaine induces lever pressing behavior only when cocaine levels are below the satiety threshold and above the priming threshold, a range termed the compulsion zone. It was demonstrated that a continuous infusion of cocaine that maintains steady state levels at or above the satiety threshold stopped cocaine self-administration behavior in rats. The cocaine analogue, WIN 35,428, was also self-administered but at a rate approximately 43-fold lower than cocaine. The lower self-administration rate of WIN 35,428 is the product of a 6-fold longer elimination half-life and 7-fold lower satiety threshold (higher pharmacodynamic potency) than that of cocaine. We hypothesized that a continuous infusion of WIN 35,428 that produces a steady-state level above the WIN 35,428 satiety threshold will stop self-administration of cocaine.
Methods: Rats were trained to self-administer cocaine intravenously on a fixed ratio 1 schedule. A Y-catheter had one arm connected to the lever-operated self-administration pump and the other arm was connected to an operator-controlled continuous infusion pump. Rats self-administered cocaine at a unit dose of 750 nmol/kg for 82.8±3.7 minutes. A continuous infusion of cocaine or WIN 35,428 at an average rate of 1231±120.9 nmol/kg min-1 or 19.9±0.8 nmol/kg min-1 (with a loading dose of 800 nmol/kg), respectively.
Results: Cocaine self-administration behavior stopped for the duration of the infusion for both cocaine and WIN 35,428. Self-administration behavior resumed when the infusion was ended for both treatments; however, at the end of the WIN 35,428 infusion the inter-injection intervals were longer, but gradually approached baseline.
Conclusions: An infusion of WIN 35,428 62-fold lower than that of cocaine was equally effective at stopping cocaine self-administration. This provides a rational basis for designing a substitution therapy to mitigate the use of cocaine. Whether continuous use of stimulants in humans is safe remains to be elucidated.
Financial Support: NIDA grant U01DA050330 to ABN

Prefrontal Cortex 5-HT2A Receptor Status Governs Incubated Cocaine Seeking

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Drug Category: Stimulants
Topic: Other, Neuropharmacology

Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research
Aim: Attentional orientation to cocaine-associated cues promotes relapse in cocaine use disorder (CUD). A time-dependent escalation of cue reactivity ("incubation") during abstinence from cocaine is linked to compromised excitatory/inhibitory output of the medial prefrontal cortex (mPFC). The 5-HT2A receptor (5-HT2AR) displays basal constitutive activity and is co-expressed in glutamate (excitatory) and γ-aminobutyric (GABA; inhibitory) mPFC neurons. The 5-HT2AR inverse agonist M100907 reduces constitutive 5-HT2AR activity and may prove beneficial to correct cortical dysfunction following chronic cocaine exposure. Here, we tested this hypothesis in male rats in early and late abstinence from cocaine intravenous self-administration (IVSA) and assessed subcellular 5-HT2AR protein localization at both timepoints. Secondarily, we tested the hypothesis that mPFC 5-HT2AR genetic knockdown impairs the mPFC transcriptome consistent with disrupted excitatory/inhibitory cortical balance.
Methods: Rats achieved stability on cocaine IVSA (0.75 mg/kg/inf;3hr/day) prior to injection with M100907 (0-0.3 mg/kg; i.p) 30 min before the cue reactivity session on Day 1 or Day 30. Rats were sacrificed following the cue reactivity session for ex vivo analyses of mPFC subcellular 5-HT2AR protein expression. A separate cohort received bilateral mPFC infusions of a non-silencing control (AAV2-NSC-eGFP;n=8) or 5-HT2AR shRNA (AAV2-5-HT2AR-shRNA-eGFP;n=8); next generation sequencing and bioinformatics platforms profiled the transcriptomic impact of mPFC 5-HT2AR loss.
Results: All doses of M100907 decreased lever presses reinforced by cocaine-associated cues on Day 30 ($p<0.05$), but not Day 1. The ratio of membrane:cytosolic 5-HT2AR protein was significantly higher at Day 30 vs. Day 1 ($p<0.05$). The transcriptomic profiling of mPFC 5-HT2AR loss revealed a 1132 differentially expressed genes between NSC-eGFP and 5-HT2AR-shRNA-eGFP rats characterized by alterations in glutamatergic and GABAergic signaling.
Conclusions: Our findings suggest that regulated 5-HT2AR constitutive activity and allied cortical signaling consequent to cocaine IVSA may contribute to long-lasting cocaine cue reactivity and craving, raising the therapeutic potential for a 5-HT2AR inverse agonist to mitigate CUD relapse events.
Financial Support: T32DA007287, P50DA033935, and the Center for Addiction Sciences and Therapeutics

Selective Modulation of the Reinforcing Effects of Fentanyl by a Monoclonal Antibody in Rhesus Monkeys

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Drug Category: Opiates/Opioids
Topic: Behavioral Pharmacology
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research
Aim: In 2022, nearly 70% of drug overdose deaths were attributed to fentanyl's, indicating a high prevalence of intentional use or inadvertent exposure (adulteration of other drugs). Naltrexone attenuates the reinforcing effects of opioids by competitive antagonism at the mu-opioid receptor and is the only opioid receptor antagonist available for treating opioid use disorder (OUD). However, non-selectively inhibiting all opioid agonists at the site of action may preclude the use of opioid agonist pain medications and maintenance therapies. Highly selective fentanyl-targeting monoclonal antibodies (mAbs) may be an effective alternative as they bind and sequester fentanyl in the serum. A promising mAb has high selectivity for fentanyl in vitro, but its selectivity has not been confirmed in vivo, nor whether it attenuates the reinforcing effects of fentanyl.
Methods: The mAb was examined in three rhesus macaques self-administering drug intravenously twice per day, seven days per week. Dose-effect curves were generated for fentanyl, heroin (opioid comparator), and cocaine (non-opioid comparator). The unit dose at the peak of each curve was identified and the mean number of infusions obtained of that dose of each drug determined across three self-administration sessions (baseline). Monkeys received a single administration of vehicle or the mAb 15 min prior to a self-administration cycle in

which fentanyl was available; on subsequent days fentanyl was available in the morning and heroin or cocaine in the afternoon.
Results: The mAb significantly decreased the number of fentanyl infusions obtained, compared with baseline performance ($p<0.05$), in some monkeys for 18 days. Over the same time, the mAb did not significantly affect the number of heroin or cocaine infusions received in afternoon sessions.
Conclusions: These data demonstrate the selectivity of the mAb for attenuating the reinforcing effects of fentanyl and support further examination of its potential clinical utility as an OUD medication.
Financial Support: These studies are supported by USPHS grants U01DA051658 (MP), T32DA031115 (CPF), and the Welch Foundation (AQ-0039 [CPF]).

ORAL SESSION: BUILT TO LAST? LONG-ACTING FORMULATIONS USE DISORDERS

An Emulated Trial of Buprenorphine-Naloxone Versus Extended-Release Naltrexone Following Medically Managed Opioid Withdrawal

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Drug Category: Opiates/Opioids
Topic: Treatment
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research
Aim: Buprenorphine-naloxone (BUP-NX) and extended-release naltrexone (XR-NTX) are both efficacious medications for opioid use disorder, but data on their comparative effectiveness in reducing all-cause mortality and nonfatal opioid overdose are limited.
Methods: We conducted an observational study emulating the protocol of the X:BOT randomized controlled trial. We used individually linked administrative data from the Massachusetts Public Health Data Warehouse. Eligibility criteria were age 18+ years and discharge from medically managed opioid withdrawal (MMOW), also called opioid detoxification, from January 2014 through December 2018. Individuals could meet eligibility more than once. We compared two treatment strategies: initiation of BUP-NX versus XR-NTX within 28 days of MMOW discharge. Outcomes were all-cause death and nonfatal opioid overdose following MMOW discharge. We estimated the 24-week cumulative incidence for each outcome using inverse probability weighting to adjust for baseline and time-varying confounders.
Results: We identified 106,052 eligible episodes among 36,752 unique individuals. Of these individuals, 75% were male, 42% were aged 18-29 years, 75% identified as non-Hispanic White, and 23% reported being homeless. BUP-NX and XR-NTX were initiated within 28 days of MMOW discharge in 12,399 (11.7%) and 4,069 (3.8%) of eligible episodes, respectively. The adjusted 24-week cumulative incidence (95% confidence interval) of all-cause death post-MMOW discharge was 1.4% (1.2%,1.7%) for BUP-NX, and 1.5% (1.2%,1.8%) for XR-NTX, corresponding to a risk difference for BUP-NX versus XR-NTX of 0.0 percentage points (pp; -0.4pp,0.4pp). The adjusted 24-week cumulative incidence of nonfatal opioid overdose post-MMOW discharge was 11.9% (11.2%,12.6%) for BUP-NX, and 14.3% (13.3%,15.5%) for XR-NTX, corresponding to a risk difference for BUP-NX versus XR-NTX of -2.4pp (-1.2pp,-3.6pp).
Conclusions: Compared with XR-NTX, initiating BUP-NX after MMOW was associated with a lower risk of nonfatal opioid overdose at 24 weeks, but no difference in risk of all-cause death.
Financial Support: NIH/NIDA R01DA054268

A Prospective Observational Study in Naturalistic Settings to Describe Long-Acting Injectable Buprenorphine Introduction in France: The OBAP Cohort Study

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Drug Category: Opiates/Opioids
Topic: Treatment
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research

Aim: Long-acting formulations of buprenorphine (LAB) have been developed with promising perspectives to facilitate long-term acceptance of buprenorphine treatment, reduce misuse and diversion and potentially increase treatment response. OBAP (Long-Acting buprenorphine Observatory) is a prospective observational open cohort study started in 2023 in France by the University of Bordeaux (UB), Bordeaux, France. Main objectives are to examine, over a period of 6 months after LAB treatment initiation changes in 1) substance addiction severity; 2) quality of life, craving, opioids and other use and misuse, satisfaction with LAB.
Methods: When a patient is scheduled for LAB treatment, the prescriber sends patient telephone contact to UB. An OBAP Clinical Research Assistant (CRA), contacts the patient to present the study. After consent a baseline interview is scheduled just before first LAB administration and follow-up assessments are scheduled after 1, 2, 3 and 6 months. These interviews are based on standardized validated tools: the Addiction Severity Index (ASI), DSM5 diagnosis, quality of life (EQ-5D-5L, NHP, SF-12), treatment satisfaction (TSQM), and urine specimen.
Results: Between March 1 and December 20, 28 French treatment centers joined the OBAP study and reported 101 LAB initiations. 77 patients were reached by an OBAP CRA and 54 gave consent. Current retention in research at M1, M2, M3 and M6 is 68.3, 59.4, 45.8 and 71.4% respectively. Preliminary analysis showed notably a decrease in Composite Score of the Drug section of the ASI (main outcome) over time: average % decrease in individuals interviewed at M1, M2, M3 was -42.7, -54.2 and -69.7% respectively, compared to M0.
Conclusions: OBAP cohort study may provide a better general understanding of the clinical course and quality of life for individuals with opioid use disorder initiating treatment with LAB. These data will be useful for future clinical practice and public health regulations.
Financial Support: The University of Bordeaux is the sponsor of this research and has received funding from Camurus for the implementation of the study (agreement n°AST-CT2022-157). Camurus is the manufacturer of Buvidal® a weekly and monthly LAB formulation that is licensed in France.

Outcomes From the Randomized, Double-Blind, Placebo-Controlled Trial of Monthly Injectable Buprenorphine for Methamphetamine Use Disorder

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Drug Category: Stimulants
Topic: Treatment
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research

Aim: The current study presents findings of a 12-week multi-site trial comparing injectable buprenorphine to injectable placebo for MUD in individuals with mild opioid use disorder (OUD) or opioid misuse.
Methods: Eligible participants with moderate/severe MUD and mild OUD or opioid misuse across six sites in the U.S. were randomized to 12-weeks of monthly injectable buprenorphine (300 mg @ 4 weeks) or placebo. All participants completed a 2-3 day sublingual buprenorphine induction. The primary outcome

measure was the number of methamphetamine-negative urine drug screens during Weeks 9-12 for participants receiving either injectable placebo or injectable buprenorphine.
Results: Enrollment began March 2023 and was stopped by the DSMB September 2023 due to unacceptable sedating effects of the sublingual medication and inadequate prevalence of this group to populate the trial. Of participants who pre-screened for the study, 120 advanced to screening. The top reasons participants screened ineligible were not meeting criteria for mild OUD or opioid misuse (52% [N=53]) and not using methamphetamine for at least 18 days in the prior 30 (24% [N=24). Of 19 screened eligible, 18 randomized to medication condition. Of those randomized, 16 started sublingual induction procedures; seven completed sublingual induction and received injectable medication. Data lock is complete in January 2024 with primary and secondary outcome findings forthcoming.
Conclusions: Findings show severe methamphetamine use disorder and opioid misuse/mild OUD is not prevalent. Using buprenorphine in individuals with MUD and no opioid dependence produces sedating effects that are unacceptable for participants. While the rationale for this kappa antagonist remains reasonable, there is little evidence for using this single medication. There may be better acceptability to pairing an opioid antagonist with buprenorphine for those with severe methamphetamine use disorder and mild opioid use disorder or opioid misuse.
Financial Support: This study was supported by funds from the NIH Heal Initiative through NIDA's CCTN.

Predictors of Buprenorphine Formulation Preferences Among Individuals Experiencing Homelessness With Opioid Use Disorder

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Drug Category: Opiates/Opioids
Topic: Treatment
Abstract Detail: Other
Abstract Category: Original Research
Aim: We sought to identify correlates of willingness to take buprenorphine (BUP), and corelates of a preference for extended-release buprenorphine (XR-BUP) over sublingual formulations, among people experiencing homelessness (PEH) who had an opioid use disorder (OUD).
Methods: We recruited 310 out-of-treatment male and female adults, age< 18 years, from harm reduction programs in San Francisco, CA and administered a survey of attitudes and preferences toward buprenorphine. Odds ratios (ORs) and 95% confidence intervals (CI) were used to inform potential differences in frequency estimates. Multiple logistic regression was used to identify independent correlates of a preference for XR-BUP over sublingual BUP.
Results: Of the 310 subjects, 47 (15%) did not want either BUP formulation, while 253 (82%) preferred at least one formulation (3% missing data). Most had prior experience with BUP; 180 (71%) with sublingual BUP, and 12 (4.7%) with XR-BUP. Of the 253 subjects who preferred a buprenorphine formulation, 144 (57%) preferred sublingual BUP, and 109 (43%) preferred XR-BUP. Compared to subjects who were willing to take either BUP formulation, subjects who did not want either formulation viewed cutting back or stopping the use of opioids as less important, OR = .49 (CI: .37, .65), and they endorsed fewer positive attitudes toward sublingual buprenorphine, OR = .28 (CI: .19, .42). A preference for XR-BUP over sublingual BUP was positively associated with viewing it as more convenient, adjusted (A) OR = 12.6 (95%CI: 3.84, 41.7), but negatively associated with feeling ready to take XR-BUP (AOR = .22; CI: .10, .49), and negatively associated with a concern that they could not change their mind upon taking XR-BUP (AOR = .33; CI: .17, .65).
Conclusions: Among PEH with OUD, preferences for buprenorphine formulations were associated with perceptions of convenience, readiness to take a long-acting medication for OUD, and concerns about having control over treatment.
Financial Support: Supported by NIDA DA050038

ORAL SESSION: EXPLORING THE PARENT-CHILD DYAD: RECIPROCAL INFLUENCES AND THEIR IMPACT ON DRUG USE AND OTHER RELATED OUTCOMES

Using a Dyadic Analysis to Examine the Association Between Family Substance Use History, Attachment, and Substance Use Among Youth Involved in the Legal System and Their Primary Caregivers

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Drug Category: Polydrug (i.e. concurrent use two or more drugs)
Topic: Criminal Justice, Substance use prevention intervention
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research

Aim: Youth involved in the legal system (YILS) are at high risk of substance use (SU) and often come from families with a SU history. Intergenerational transmission of health-risk behaviors suggests that family members' (e.g., parents, grandparents, siblings) SU is a risk factor to individual SU, and such an influence may be extended to their offspring. The social-ecological model (CDC, 2022) posits that family members mutually influence the thoughts, emotions, and behaviors of one another. As such, family members' SU history may impact the child-caregiver relationship, which is in turn associated with health-risk behaviors across multiple generations. In this study, the child-caregiver relationship was assessed by the youth's attachment towards the primary caregiver and the primary caregiver's attachment toward his/her own caregiver (i.e., a grandparent figure). The current study adopted the actor-partner interdependence models (APIM) to conduct a simultaneous examination of the actor and partner effects on the associations between family members' SU, child-caregiver attachment, and individual past 12-month (12-month prior to coming to a locked facility for youth) SU across multiple generations, while controlling for youth and caregiver sex and race.
Methods: APIM provides an analytic framework for examining conceptually related variables assessed from dyadic perspectives. Actor effects refer to the associations between variables of the same individual in a dyad (e.g., associations between caregiver family SU, caregiver attachment, and caregiver SU). Partner effects refer to associations of one individual's variables to the other individual's variable in a dyad (e.g., an association between caregiver family SU and youth attachment). The current sample was comprised of 133 YILS and primary caregiver dyads (youth: 80% male, 62% minority, ages 15-18; caregivers: 12% male, 46% minority, ages 29-78).
Results: Results of APIM revealed that the model explained 18% and 9% of the variances in youth and caregiver past 12-month SU, respectively. Higher caregiver family member SU was associated with greater caregiver attachment avoidance and anxiety (actor effects). Youth family member SU, youth attachment avoidance, and being female were associated with more severe youth SU (actor effects). Youth attachment avoidance was associated with caregiver SU severity (partner effect). The APIM analyses also revealed that caregiver family SU was positively associated with youth family SU.
Conclusions: The findings suggested the influence of family SU on caregiver attachment and youth SU, respectively. The findings collectively underscore the context of interconnected family units being an important prevention and intervention marker for SU.
Financial Support: 1UH3DA050250

Untreated Substance Use Disorders Among Caregivers With Children Reported to Child Protective Services

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[1]*RTI International*

Drug Category: Other, substance use disorders
Topic: Policy
Abstract Detail: Clinical - Epidemiology

Abstract Category: Original Research
Aim: Untreated parental substance use disorders (SUD) can have profound effects on children including neglect and maltreatment. A large portion of child protective services (CPS) involvement in families and CPS-ordered child removals involve parents with SUD. The aim of this study was to determine whether caregivers with SUD, whose children were referred to CPS, received Medicaid-funded SUD treatment.
Methods: The study used the Child and Caregiver Linked Utilization and Outcomes Database (CCOULD) which contains child welfare records linked with Medicaid enrollment and claims data in Kentucky and Florida on 1,087,763 children and 89,871 caregivers for the periods January 2017 through June 2021 in Florida, and January 2017 through January 2020 in Kentucky. Medicaid claims were analyzed to determine if caregivers had a SUD and whether those caregivers received counseling or medications, overall and by black and white race.
Results: In 2020, 42% of caregivers with Medicaid and children referred to CPS had SUD, as compared to 12% of age/gender matched Medicaid beneficiaries without children referred to CPS. Among caregivers with Medicaid, children referred to CPS and a SUD, 42% received counseling and 38% received a SUD medication. Medicaid beneficiaries who were Black with children referred to CPS were less than beneficiaries who were White to receive counseling (45% versus 23%) or medications (42% versus 11%, $p > 0.01$)
Conclusions: Despite Medicaid coverage of an array of effective SUD treatments, large portions of caregivers with Medicaid coverage, who need treatment and whose children were referred to CPS, are not receiving treatment. The treatment gap was significantly greater among Black individuals than White individuals. Medicaid and child welfare agencies need to make a greater effort to connect caregivers to SUD services.
Financial Support: Office of the Assistant Secretary for Planning and Evaluation, Department of Health and Human Services

Evaluating Caregiver Acceptance of Inpatient Pediatric Clinician Screening for Family Substance Use

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Drug Category: Other, All substance use types within a family
Topic: Prevention
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research
Aim: Exposure to parental substance use (SU) is an adverse childhood experience that places children at greater risk for mental and physical health co-morbidities, including future SU. Despite guidelines, pediatricians rarely screen for SU in the family/household, citing fear of offending parents as a barrier. Prior studies found caregiver acceptance of universal screening for family/household SU during pediatric outpatient visits, but it is unclear if caregiver preferences may differ in other clinical settings. The current cross-sectional study assesses caregiver acceptance of screening for family/household SU during pediatric hospital admissions.
Methods: In this IRB-approved study, English-speaking adult caregivers of pediatric patients admitted to a community hospital in Baltimore, Maryland, completed an anonymous computer-based survey. Trained research staff enrolled patients and facilitated data collection on six single-item measures to assess the acceptability of inpatient screening for family/household SU and current household SU. Based on sample size and power calculations, target enrollment is 275 caregivers. Preliminary data was evaluated using descriptive statistics.
Results: The interim sample included 87 caregivers, most of whom were aged 31-40 (52%), Black (48%), and mothers (64%). Over 33% of caregivers reported SU in the family/household, primarily alcohol (21%), tobacco (9%), and marijuana (8%). Ninety-four percent of caregivers had no concerns about discussing family/household SU with their child's inpatient pediatrician, while 6% declined to answer. The majority of participants agreed that it was important for inpatient pediatricians to ask about household SU, ranging from 85%-89% across substance types. Seventy-six percent of caregivers would want to receive resources from inpatient pediatricians if they had concerns about household SU.

Conclusions: Preliminary findings suggest caregivers are amenable to universal screening for family/household SU during pediatric hospital admissions and would accept resources when concerns exist. Ongoing analysis will assess differences in SU screening acceptability based on current SU in the family/household and trust in the inpatient providers.
Financial Support: R25DA03321, T32HD052459

Mothers and Fathers who Use Medical Cannabis: A Comparison of Sociodemographics, Mental Health, and Cannabis Use

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Drug Category: Cannabis/Cannabinoids
Topic: Sex/Gender Differences
Abstract Detail: Other
Abstract Category: Original Research
Aim: With ongoing cannabis legalization in the U.S., an increasing number of parents are becoming legitimate medical cannabis patients. Prior research however has extensively focused on parents' recreational cannabis use. This highlights the need to assess and compare sociodemographic, mental health, and cannabis use characteristics between mothers and fathers who use medical cannabis.
Methods: 290 Pennsylvania-based medical cannabis patients who identified as parents living with their children were recruited and surveyed between June 2021 - November 2023. Gender differences were evaluated using logistic regression and Poisson regression, controlling for age and race.
Results: The sample comprised 62.8% mothers and 37.2% fathers. Differences in age (sample mean=41.5 y.o.), race (78.6% White) or current employment rate (74%) were non-significant. However, a significantly lower proportion of mothers (67.8%) than fathers (80.6%) were married or had a monogamous partner. Compared to fathers, mothers had lower exposure to any arrest (22.5% vs. 61.3%), cannabis possession arrest (7.1% vs. 25.0%), or lifetime opioid misuse (28.6% vs. 44.4%). While the frequency of cannabis use was comparable between mothers and fathers (averaging 76.1 vs. 77.6 days in the past 90 days), mothers consumed less cannabis per day, spent less money on cannabis, and had a lower problematic cannabis use score. Mothers, however, had higher prevalence of lifetime PTSD (39.0% vs. 25.9%), higher scores on both anxiety (GAD-7) and depression (PHQ-9) and were more likely than fathers to report that anxiety and depression interfered with everyday functioning.
Conclusions: Despite less involvement with criminal justice system, lower rates of opioid misuse and lower level of problematic cannabis use, mothers who used medical cannabis had a more adverse mental health profile than fathers. Future research should delineate how lifetime trauma, single parenting and potential self-stigmatization due to cannabis use contribute to the ongoing mental health challenges faced by mothers who participate in medical cannabis programs.
Financial Support: The study is funded by a multi-year research agreement between Drexel University and Agronomed Biologics, which is owned by Verano (a multi-state cannabis company).

ORAL SESSION: SMOKE SIGNALS: DECODING THE BRAIN'S RESPONSE TO NICOTINE CUES

Measuring Attentional Bias towards Smoking Cues in E-Cigarette Users who Formerly or Currently Smoke Cigarettes

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[1]*Centre for Addiction and Mental Health, University of Toronto*

Drug Category: Nicotine/Tobacco
Topic: Substance Use Disorder
Abstract Detail: Clinical - Experimental

Abstract Category: Original Research

Aim: Attentional bias (AB) is the automatic allocation of attention towards substance-related cues and is a well-documented behavioural feature of tobacco use disorder. However, limited information exists on the effects of e-cigarette use on AB to smoking cues in current and former smokers. Given growing recommendations of e-cigarettes for smoking cessation, it is important to understand their effect on the behavioural features that may contribute to maintaining smoking behaviour or risk of relapse. This study aimed to evaluate the differences in AB between groups of: cigarette smokers (n=59); e-cigarette users who currently smoke cigarettes (dual-users; n=34); e-cigarette users who formerly smoked cigarettes (full-switchers; n=27); and healthy controls (n=65), using a free-viewing eye-tracking apparatus. We hypothesized that participants who had partially or completely switched to e-cigarettes would have decreased AB towards smoking cues compared to cigarette smokers.

Methods: Eligible participants attended a single study session where they were presented with a series of slides displaying 4 images on the screen at once. Images were related to either smoking, sensation seeking, affective or neutral cues. Eye-movements during the slide show were tracked and recorded using Visual Attention Scanning Technology (VAST). The primary outcome measured was mean relative fixation time (mRFT) directed towards smoking cues minus mRFT directed towards neutral cues. Participants also completed questionnaires.

Results: Independent sample t-tests showed that mRFTs towards smoking cues were significantly higher than healthy controls (0.012±0.096) for cigarette smokers (0.092±0.116), full-switchers (0.092±0.091) and dual users (0.099±0.102) (all $p<0.05$), with no significant difference between cigarette smokers and e-cig users. There were also no observed sex differences.

Conclusions: Our findings suggest that e-cigarettes do not decrease AB towards smoking cues among current or former smokers, indicating that these individuals may still be at risk for smoking relapse. Further confirmation is required by investigating AB in long-term former smokers with no e-cigarette use.

Financial Support: This research is supported by graduate fellowships from the INTREPID Lab at CAMH and the University of Toronto.

Investigating the Effects of Cue-Reactivity in Young Adult Vapers Using Functional Mri

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[1]*Centre for Addiction and Mental Health*

Drug Category: Nicotine/Tobacco
Topic: Neurobiology/Neuroscience, Neuroimaging
Abstract Detail: Other
Abstract Category: Original Research

Aim: Vaping devices containing nicotine are considered high-risk when used by young adults who have never smoked tobacco due to health effects including purported effects on the developing brain. Considering role of drug-related stimuli in the maintenance of addictive behaviours, this study aimed to determine if vaping-related stimuli drives vaping cravings, and neural activations within young adults who vape in the same way that smoking-related stimuli are known to affect adults who smoke tobacco.

Methods: Adults (age 18-25) who vape nicotine daily, (target n=25) completed two MRI scans (once abstinent, once sated). A series of validated visual vape-related, cigarette-related, and neutral cues were shown to participants in a block design. fMRI data were analyzed by fitting a general lineal model to the data time-series at every voxel across the brain and assessing effects using F/t-tests and percent BOLD signal change calculations using cluster-wise inference.

Results: In the nicotine abstinent state, higher BOLD activations were observed in the frontal pole, left cerebral cortex, precuneous cortex, supracalcarine cortex, supramarginal gyrus, and angular gyrus when presented with vaping cues compared to neutral cues (z threshold< 2.5, corrected significance threshold p=0.05). In the nicotine abstinent state, higher BOLD activations were observed in the frontal pole, superior frontal gyrus, left cerebral cortex, left thalamus, paracingulate gyrus, superior frontal gyrus when presented with vaping cues compared to smoking cues (z threshold< 2.5, corrected significance threshold p=0.05).

Conclusions: This is the first study to use a whole brain approach to examine functional brain alterations in young adults who vape but have never smoked. The complete data set will explore the effects of nicotine abstinence or satiety on cue reactivity, and compare to healthy controls or adults who smoke tobacco.
Financial Support: Graduate fellowships from the INTREPID Lab at CAMH and the University of Toronto.

10 Hz Excited DLPFC, but Not 1 Hz Inhibited Mofc Induced Smoking Cessation: A Randomized Repetitive Transcranial Magnetic Stimulation Trial

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Drug Category: Nicotine/Tobacco
Topic: Treatment, fMRI
Abstract Detail: Other
Abstract Category: Original Research
Aim: To understand repetitive magnetic stimulation (rTMS) effects on addiction circuits and potentially identify a more effective rTMS treatment protocol (1 Hz over medial orbitofrontal cortex [mOFC] vs. 10 Hz over dorsolateral prefrontal cortex [DLPFC]) for smoking cessation.
Methods: Treatment-seeking tobacco use disorders randomly received one of the following three rTMS treatments: 1) Sham rTMS over either the left mOFC or the left DLPFC. 2) Active 1 Hz rTMS over the left mOFC (1 Hz, 900 pulses, personalized E-field dosing, 15 minutes). Or 3) Active 10 Hz over the left DLPFC (10 Hz, 3000 pulses, personalized E-field dosing,15 minutes). Cue-craving and resisting functional MRI scans were completed before and after 3-week rTMS treatment. Cigarette per day (CPD) was a primary clinical outcome. Connectivity between brain regions was the primary outcome for neuroimage measures. The project was performed from May 15, 2021, to July 14, 2023.
Results: We enrolled 46 participants and analyzed the 36 completers' data (sham group = 9, active mOFC group = 15, active DLPFC group = 12). 10 Hz rTMS over the DLPFC reduced cigarette consumption and was superior to the mOFC site as well as the sham treatment.(sham: -6.43[0.54]; 10 Hz DLPFC: -11.14[0.48]; 1 Hz mOFC: -4.92[0.43]; $F(2,623) = 48.65$, $p > 0.0001$). 10 Hz rTMS inhibited the acute cravings to respond to a cue provocation.10 Hz increased the strength of the connection between the DLPFC and the nucleus accumbens (0.48 vs. 0.61) and the connection between DLPFC and mOFC (0.50 vs.0.60). 10 Hz rTMS decreased brain activity in mOFC and increased brain activity in DLPFC.
Conclusions: 10 Hz DLPFC rTMS is superior to 1 Hz mOFC site and sham treatment. The 10 Hz DLPFC treatment also modulated the reward and executive control circuits.
Financial Support: NIDA/DA048507

The Autonomic Craving Signature: A Pattern of Physiological Signals Associated with Craving in Daily-Life among tobacco, Alcohol and Cannabis Users with Sud

Emmanuelle Baillet-Gaborieau*[1], Fuschia Serre[1], Hakim Si-Mohammed[2], Alexis Chevalier[1], Thibaut Monseigne[1], Camille Jeunet-Kelway[1], Marc Auriacombe[1]

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Drug Category: Nicotine/Tobacco
Topic: Substance Use Disorder
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research
Aim: Among the 11 DSM-5 SUD symptoms, craving, a strong urge to use, is the most central, discriminant and prevalent. Fluctuations of craving intensity have been prospectively associated with use, making it a target for treatment. However, to be examined, craving needs to be self-reported, which limits long-term monitoring and requires cognitive abilities that may be impaired. Ecological momentary assessment (EMA) overcomes memory bias by repetitive assessment on smartphones in daily life. Cue reactivity Laboratory studies have shown that craving is associated with physiological variations that can now be continuously monitored in daily

life. The aim was to identify craving through the analysis of physiological signals captured in daily life, opening the way to biomarkers of craving.
Methods: In a 14-day observational mixed methods study in daily life among individuals with a variety of SUD we combined wearable sensors (Blood Volume Pulse, Electrodermal Activity, skin temperature, accelerometry) with EMA for signal- (4 times/day) and event-contingent (triggered by the participant) surveys. We used principal component analysis (PCA) to reduce dimension space of features extracted, machine learning algorithms to discriminate craving from no-craving periods and permutation test.
Results: 45 subjects were included. EMA completion rate was 85.8% (n=2,017) and 5,512 hours of physiologic data were captured over the course of 14 EMA-days. 384 samples of "craving" (n=192) and "no-craving" (n=192) were analyzed by PCA in which 31 principal components explained 98.8% of variance data. We tested 3 different classification algorithms with which we reached between 58.3% and 73.6% of accuracy.
Conclusions: Performance of our binary classification model was better than a random binary classifier (i.e.: AUC-ROC< 0.55) and this set of features forms a physiological pattern that can distinguish craving from no-craving states and that we labeled the autonomous craving signature (ACS).
Financial Support: Institut National du Cancer and Institut de Recherche en Santé Publique (INCa-IReSP_15746) and in the framework of the University of Bordeaux's IdEx "Investments for the Future" program/GPR BRAIN_2030 (Adapsy project).

Wednesday, June 19, 2024

ORAL SESSION: IN UTERO INSIGHTS

Maternal Opioid Exposure Alters Murine Neurodevelopment

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Drug Category: Opiates/Opioids
Topic: Neurobiology/Neuroscience
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research
Aim: Over 111,000 opioid-involved deaths in the U.S. were reported in the year ending in April 2023. Maternal opioid related diagnoses have increased 131% from 2010 – 2017. A challenging problem is related to pregnant opioid use disorder (OUD) patients stabilized on buprenorphine (BUP). OUD management during pregnancy must be balanced against the potential for opioid-evoked developmental defects. We recently discovered that mouse dams treated with oxycodone (OXY) before pregnancy and BUP throughout gestation (OXY+BUP) resulted in abnormal brain neurogenesis in offspring coupled to sex-dependent behavioral sequelae. We are investigating the causal mechanisms underlying maternal opioid exposure and offspring function. In the present study, we tested the hypothesis that maternal opioid exposure with BUP management alters neurogenesis at the early developmental stage, embryonic day 13.5 (E13.5).
Methods: The estrus cycle of adult female C57BL/6J mice was tracked and saline or OXY (20 mg/kg) treatment per os began seven days prior to mating. Upon proof of copulation, saline or OXY treatment continued or OXY was switched to BUP (0.5□4 □g/g, ramping dose; BUP+OXY) to simulate treatment of OUD. Embryos were collected at E13.5 and sectioned at 30 □m. Immunohistochemistry (Sox2, SATB2, Ki67, Ctip2, OTX2/TH) was conducted and cell count/density in medial prefrontal cortex (mPFC), amygdala, and ventral tegmental area (VTA) was quantified (ImageJ).
Results: OXY+BUP exposure during pregnancy altered in utero brain development, specifically increasing mPFC (Ctip2+) ($F_{5,2}=24.02$, $p=0.04$; n=1-2) and amygdala (SATB2+) thickness ($F_{5,2}=25.11$, $p=0.04$; n=1-

2) in male and female mice vs. controls. There is a trend for OXY+BUP treatment to increase dopaminergic cell count (Otx2+/TH+) in the VTA vs. controls (n=1).
Conclusions: These experiments demonstrate that maternal OXY+BUP treatment may have detrimental impact on early brain development. Continuing investigations are focused on establishing the risks of in utero OXY+BUP on brain and behavior of adolescent and adult mice.
Financial Support: This project is supported by the National Institutes of Health (R01 DA050871), John S. Dunn Research Foundation, Center for Addiction Sciences and Therapeutics, and T32DA07287.

Causally Linkage of Adolescent Behavioral Anomalies to Prenatal Opioid Exposure

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Drug Category: Opiates/Opioids
Topic: Prenatal/Perinatal
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research
Aim: Maternal opioid-related diagnoses increased by 131% from 2010 to 2017, leading to an 82% rise in neonatal abstinence syndrome. The medication for opioid use disorder (OUD) buprenorphine (BUP), a partial mu-opioid agonist, maximizes health outcomes of mothers and their newborns. However, there is a critical need to investigate potential risks related to BUP that could lead to opioid-evoked congenital defects. Our novel murine model employs a clinically relevant regimen of oral administration of oxycodone (OXY) before pregnancy and BUP throughout gestation to mouse dams. In the present study, we tested the hypothesis that maternal opioid exposure leads to aberrant behavior in offspring.
Methods: C57BL/6J dams were exposed to OXY for seven days prior to mating. Upon confirmation of pregnancy, dams received oral VEH+VEH, OXY+BUP or OXY+OXY throughout gestation. After weaning on postnatal day (PND) 21, offspring were group-housed. On PND60, anxiety-like behavior was assessed in the elevated plus maze (EPM) via time spent in closed and open arms. On PND61, spontaneous locomotor activity (LMA) was evaluated in an open field. On PND62-66, the novel object recognition (NOR) test was employed to assess memory. All behavioral assays were conducted in low-light conditions and analyzed using one- or two-way analysis of variance, as appropriate.
Results: We observed decreased time spent in open arms of the EPM in adolescent offspring (n=46) from dams exposed in utero to OXY+OXY or OXY+BUP ($p<0.05$). In addition, we observed increased (OXY+OXY) or decreased (OXY+BUP) LMA, respectively, at specific timepoints ($p<0.05$). There was a non-significant trend toward decreased recognition memory in the NOR assay in mice exposed to in utero opioid treatment.
Conclusions: In utero exposure to OXY+OXY and OXY+BUP resulted in altered adolescent behaviors suggestive of anxiety-like behavior, disrupted motor activity and possibly memory alterations. Ongoing studies are focused to understand the full phenotypic and neural risks of in utero OXY/BUP on adolescent and adult mice.
Financial Support: R01DA050871, T32DA07287

Prenatal Fentanyl Exposure Affects Fentanyl-Induced Respiratory Depression and Antinociception in Adult Offspring

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Drug Category: Opiates/Opioids
Topic: Prenatal/Perinatal
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research

Aim: Fentanyl abuse during pregnancy is a rising health concern, as there is only limited knowledge of the long-term effects on offspring. In the present preclinical study, we investigated how high-dose prenatal exposure to fentanyl via maternal self-administration affected adult offspring's reactivity to the respiratory depressant and antinociceptive effects of fentanyl bolus doses compared to effects in control offspring.
Methods: Offspring from dams that had daily access to fentanyl self-administration throughout pregnancy (fentanyl-exposed), or saline-yoked dams (controls) were experimentally naïve and tested at the age of 12-14 months. The respiratory depressant effects of bolus doses of fentanyl were assessed using whole body plethysmography. Fentanyl-induced antinociception was determined in a thermal assay, using a different cohort of prenatally-exposed and control offspring.
Results: Fentanyl induced dose-dependent respiratory depression in adult prenatally fentanyl-exposed and control offspring, with respiratory depression occurring in fentanyl-exposed offspring at lower doses than controls. Fentanyl induced dose-dependent analgesia in fentanyl-exposed and control offspring, but fentanyl-exposed offspring required higher doses for full analgesic effects. In control offspring there was no overlap between fentanyl doses that induced respiratory depression and those that resulted in full analgesia. In fentanyl-exposed offspring, doses that already induced significant respiratory depression, were not fully efficacious as analgesics.
Conclusions: These results indicate that prenatal fentanyl exposure alters the sensitivity to the respiratory depressant and antinociceptive effects of fentanyl compared to controls. Importantly, fentanyl doses that are required to produce analgesia are also inducing respiratory depression in fentanyl-exposed offspring. In control offspring however, the full analgesic effect is reached with doses that do not induce respiratory depression.
Financial Support: NIH/NIDA R21DA052801, NIH/NIDA R01DA059181, NIH/NIGMS 5P20GM121334

Identification of Epigenetic Biomarkers Associated With Prenatal Exposure to Substances of Abuse

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Drug Category: Polydrug (i.e. concurrent use two or more drugs)
Topic: Prenatal/Perinatal
Abstract Detail: Other
Abstract Category: Original Research
Aim: The purpose of this project is to establish the feasibility of using epigenetic profiles to differentiate newborns with in utero illicit drug exposure and non-exposed newborns using DNA extracted from neonatal blood spots. The ultimate goal of this research is to validate an epigenetic biomarker of fetal exposure to illicit drugs that is predictive of the associated developmental consequences.
Methods: In total 299 mother/newborn dyads were enrolled from our site at the Charleston Area Medical Center Women and Children's hospital. Data collected included the infants' gender, maternal risk factors, infant payer group, growth parameters, estimated gestational age at time of delivery, Apgar scores, need for NICU care, NAS diagnosis and severity, and results of prenatal alcohol and other substance exposure testing. Newborn heel stick dried blood spots were collected. From the 299 women that were enrolled in this study, 128 newborn samples were selected for examination of their whole epigenome methylation patterns.
Results: The primary question of the current research project is whether it is feasible to identify differential methylation patterns between substance exposed newborns (n = 80) and non-exposed control newborns (n = 48). Differential methylation analysis between these two groups identified 242 CpG methylation sites that are statistically different (p values from 4.9E-09 to 3.0E-05) between exposed and non-exposed controls. The percent methylation differences identified between positive exposed versus negative control samples was between -5.3% and +5.7%, with the percentage change (fold change) in these groups ranging from -46.5% to +21.4%.
Conclusions: Current efforts are now focused on looking into multiple other analyses including: the methylation patterns of THC positive only versus THC plus other drugs and the THC negative exposed group, single drug class methylation patterns versus negative exposed group; and the methylation patterns of the polysubstance exposed group versus the negative exposed group.
Financial Support: NIDA 1R43DA054030

ORAL SESSION: SMOKE-FREE SOLUTIONS: CUTTING-EDGE TREATMENTS FOR NICOTINE DEPENDENCY

A Functional Approach to Smoking Cessation for People with Intellectual Disabilities

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Drug Category: Nicotine/Tobacco
Topic: Behavior
Abstract Detail: Other
Abstract Category: Original Research

Aim: There is a concerning lack of published smoking cessation research on people with Intellectual and Developmental Disabilities (IDD). A Functional Assessment for Smoking Treatment Recommendations (FASTR) was recently developed to help personalize patients' treatment and identify skills needed to decrease their smoking. Adapting this tool to effectively evaluate/determine putative environmental variables that maintain smoking for people with IDD is predicted to improve current treatments. The purpose of this study was to introduce the FASTR to a small sample of people with IDD who smoke cigarettes using a qualitative approach.
Methods: During one-hour interviews, participants (N = 8) described the extent to which they agreed with each FASTR statement, which corresponded to one of five potential functions of smoking (i.e., Automatic Positive, Automatic Negative, Social Positive, Social Negative, and Antecedent). Participants provided examples of how each statement applied to their smoking behavior and suggestions for how to make the assessment more inclusive of people with IDD.
Results: Seven participants had difficulty with at least one specific word (e.g., interact, demanding). Five participants reported having difficulty with the Likert scale, which was modified to yes or no questions for two of those participants. Participants recommended making the subject of each statement larger font and in bold so respondents can understand the most important part of the statement. Participants primarily endorsed statements categorized as automatic negative reinforcement and rarely endorsed automatic positive statements.
Conclusions: The FASTR was modified based on participant feedback and will be distributed to a larger sample of people with IDD. Ongoing research is determining the ability of the modified FASTR to improve function-based smoking cessation interventions in this population.
Financial Support: This research was supported by a pilot grant from the University of Kentucky's Department of Behavioral Science and grants from the NIH (T32DA035200; TL1TR001997).

Coordinating Smoking Cessation Treatment with Menstrual Cycle Phase to Improve Quit Outcomes: A Randomized Controlled Trial

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Drug Category: Nicotine/Tobacco
Topic: Sex/Gender Differences
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research

Aim: Women experience greater difficulty quitting smoking compared to men. This online clinical trial investigates whether targeting the quit date to the follicular or luteal phase of the menstrual cycle can improve smoking abstinence. We hypothesize that people who quit in the mid-follicular phase will have the highest quit rates compared to treatment as usual (TAU).

Methods: Naturally cycling individuals (target n=1200) are randomized to set a target quit date either: 1) during the mid-luteal phase; 2) during the mid-follicular phase, or; 3) 15-60 days after enrolment with no regard to cycle phase (TAU). Participants receive a 6-week supply of nicotine replacement therapy and start the quit attempt on their assigned target quit date. Dried blood spots are collected to confirm smoking status and menstrual cycle phase at baseline, 7 days, 6 weeks, and 6 months post-target quit date. Quit outcomes will be compared between groups using logistic regression models with adjustment for age, income, and heaviness of smoking.
Results: There are currently 240 participants in the study, age 33.4±5.3 years, smoking 16.2±7.9 cigarettes per day at baseline. 43.3% have completed the 7-day follow-up. Self-reported 7-day point prevalence of smoking abstinence (7-day PPA) was 33.3% in the TAU and mid-luteal groups and 27.6% in the mid-follicular group. At the end of treatment (respondent n=58), the 7-day PPA was 34.8% in the TAU group, 66.7% in the mid-follicular group, and 30% in the mid-luteal group. To date, 26 participants have completed the 6-month follow-up, with 30-day PPA of 30.8%. Expanded results will be presented at the meeting.
Conclusions: Results of the clinical trial will further elucidate the effects of menstrual cycle on smoking cessation outcomes and help close the observed sex gap in quit outcomes.
Financial Support: This study is funded by the Canadian Cancer Society (Award# 707321), with student support from University of Toronto.

A Quality Improvement Incentive-Based Program with Micro-Randomized Messages to Improve Smoking Cessation in Low-Resource Populations

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Drug Category: Nicotine/Tobacco
Topic: Treatment
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research
Aim: In the United States, smoking remains a leading cause of preventable death. Individuals with a greater number of socioeconomic- and health-related disparities smoke at higher rates. We present a pilot program that uses a smartphone-delivered incentive-based treatment to help low-resourced individuals quit smoking. We evaluate preliminary outcomes from the program and the embedded pilot micro-randomized trial (MRT) designed to micro-randomize whether participants received a message to promote intrinsic motivation.
Methods: We conducted a community-based MRT where participants were sent up to two messages a day (morning/evening) for four weeks. At each time point, there was a 50% chance a message would be sent. Smoking was assessed through carbon monoxide (CO) measurement twice daily (morning/evening) for four weeks; abstinence (CO level ≤ 6 parts per million [PPM]) was incentivized. We evaluate changes in smoking measured by CO immediately after the four-week intervention and estimate the effect of messages on proximal CO level.
Results: Participants (n=37) were Medicaid beneficiaries and micro-randomized at 2,072 decision points. Participants were on average 39.5 (±10.8) years old; the majority had a yearly income of>$15,000 (63.9%) and were female (58.3%). Overall, messages were sent to participants at 48.1% of decision points and 69.5% of breath samples were submitted. Immediately following the intervention, 77.4% of participants reduced smoking and 61.3% had quit (maintained CO level of ≤ 6 PPM). The estimated effect of messages on proximal CO level was not significant (T2 = 1.22; p = 0.28).
Conclusions: Preliminary findings support the use of digital incentive-based treatments to improve smoking cessation outcomes in low-resourced community-based healthcare settings. Designs informed by MRTs hold promise to enhance intrinsic motivation during incentive-based treatments.
Financial Support: The study was funded through internal funding and MDHHS funding. DCT's time was supported by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) T32AA007477. LNC's time was supported by NIAAA K23AA028232.

A YOUTH-FOCUSED, VIRTUAL, E-CIGARETTE CESSATION INTERVENTION COMBINING IN-PERSON CBT WITH INCENTIVES

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Drug Category: Nicotine/Tobacco
Topic: Treatment
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research

Aim: Many youth who use e-cigarettes want to quit but there are few empirically validated, youth-focused e-cigarette interventions. We conducted a virtual RCT that provided Cognitive Behavioral Therapy (CBT) in combination with incentives that were contingent or non-contingent on e-cigarette abstinence to youth.
Methods: Youth (aged 13-20) who used e-cigarettes regularly (at least 4 days/week; urine cotinine levels< 200 ng/ml) and wanted to quit participated in a 6-week trial. They received remote weekly CBT sessions provided by therapists who were trained and supervised using a youth-focused CBT manual. Starting on quit day participants used an online program (NuRelm, Inc.) to provide salivary cotinine test videos every other day for the 1st 2 weeks, then 2x per week for the remaining period, and were randomized to receive incentives that were contingent (salivary cotinine> 30ng/ml) or non-contingent (providing salivary samples) on abstinence. Follow up appointments were conducted at 1, 3, 6 and 12 months after the end of treatment. The primary outcome was 7-day point-prevalence abstinence at the end of treatment (self-reports verified biochemically using saliva cotinine> 30 ng/ml).
Results: 109 participants (51 M, 52 F, 2 non-binary, 4 other; M=17.6 years old; using e-cigarettes on 6.6 + 1.10 days/week; baseline urine cotinine level of M=1371.9+1082.7 ng/mL) were randomized. Randomized starters (n= 106) completed 62% of the required 12 salivary cotinine tests, 85% of the 6 CBT sessions, and 86% provided end of treatment (EOT) outcomes. Biochemically confirmed self-reports of abstinence at EOT are at 37%; results by treatment group will also be presented. To date, 77%, 78%, 82% and 75% of participants have completed 1, 3, 6 and 12 month follow up appointments, respectively.
Conclusions: Interventions combining CBT and incentives are feasible and effective at reducing e-cigarette use among youth.
Financial Support: American Heart Association ENACT grant 20YVNR35460041

ORAL SESSION: BIO-BEACONS: ILLUMINATING DRUG USE WITH BIOSENSORS

Using Wrist-Worn Alcohol Biosensors to Detect Drinking across Lab and Field Settings

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Drug Category: Alcohol
Topic: Technology (e.g., mHealth)
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research

Aim: Transdermal technology offers potential for continuous, unobtrusive assessment of alcohol consumption. Yet to date transdermal devices have taken the form of relatively bulky ankle bracelets characterized by sparse sampling intervals. Thus questions have been raised about the suitability of transdermal technology for real-time detection of drinking and longer term wear among general populations. The current research is the first large-scale study to test the suitability of transdermal sensor technology for detecting drinking episodes in real-time.
Methods: Healthy drinkers (N=100) attended three laboratory sessions, during which they received low (.03%), moderate (.06%) and high (.09% target BAC) alcohol doses. All participants also provided breathalyzer readings in real-world contexts over 14 days. Throughout the study, participants wore a compact smartphone-integrated wrist sensor that detects alcohol passively via insensible perspiration and features rapid

sampling capabilities. Machine learning models predicted drinking vs abstinence in real time using transdermal readings collected prior (and not subsequent) to BAC readings.
Results: The final dataset consisted of 11,628 unique breathalyzer readings (5,905 from field contexts; 7,340 GREATER THAN 0.00%). Models indicated an area under the receiver operating characteristic curve (AUROC) of 0.974 (95%CI, 0.972-0.976). Analyses yielded strong sensitivity and specificity, indicating the model capable of correctly detecting 82% of true positive and 98% of true negative BAC values. When data from field (i.e., real world) contexts was examined separately, accuracy metrics were similarly strong: AUROC=.960 (95% CI, .954, 964), sensitivity 60%, specificity 99%.
Conclusions: Results indicate excellent accuracy for a new generation of new-generation wrist-worn transdermal sensor in detecting real-time drinking in everyday contexts. A compact device capable of detecting drinking episodes in real-time has a variety of uses, including for the purposes of just-in-time-adaptive-intervention, relapse prevention, long term health tracking, and clinical research.
Financial Support: This research was supported by National Institutes of Health Grants R01AA025969 and R01AA028488 to Catharine E. Fairbairn.

Bidirectional Relationships between Sleep Quality and Nicotine Vaping: A Real-Time and Real-Life Study Using Smartphones and Smartwatches

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Drug Category: Nicotine/Tobacco
Topic: Technology (e.g., mHealth), behavior
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research
Aim: Existing studies on the relationship between sleep quality and nicotine vaping are cross-sectional surveys that rely on subjective, retrospective reports on both. This study fills the literature gap by pursuing two aims: 1) examining the association between objective measures of sleep quality and a subjective report of tiredness right after waking up; and 2) investigating bidirectional relationships between sleep quality and nicotine vaping based on real-time and real-life data.
Methods: Thirty-five college students who used e-cigarettes daily wore smartwatches 24/7 for 7 days and reported about e-cigarette use via their own smartphones in real time and real life. Linear mixed models were employed to examine (1) whether 6 sleep quality indices derived from physiological data predicted subjective feeling of tiredness in the next morning; (2) whether the sleep quality from last night predicted vaping frequency, negative mood, and craving over the course of today; and (3) whether today's vaping frequency predicted the quality of tonight's sleep. A follow-up open-ended survey was conducted to explore the potential to use sleep quality as a motivator for future vaping cessation intervention.
Results: A lower overall sleep quality score predicted a higher level of tiredness in the next morning (β=-0.011,p=0.034). A higher percentage of wake time after sleep onset predicted higher levels of negative mood (β=3.979,p=0.022) and craving for e-cigarettes (β=3.081,p=0.028). A higher frequency of e-cigarette use predicted a lower overall sleep quality score (β=-0.206,p=0.032) and a higher percentage of time in light sleep (β=0.001,p=0.030). The majority of participants realized their sleep problems and actually higher frequency of vaping.
Conclusions: The findings of this first real-time and real-life study support bidirectional relationships between sleep quality and nicotine vaping. Smartwatch and smartphone technology has shown promise for future vaping cessation intervention.
Financial Support: This work was supported by the National Institutes of Health (R01DA049154).

Small Business Program: Scalable Neurofeedback to Address Cue-Induced Craving in Opioid Use Disorder Treatments

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Drug Category: Opiates/Opioids
Topic: Technology (e.g., mHealth), Neurofeedback, Biofeedback
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research
Aim: Individuals with Opioid Use Disorder (OUD) often experience "cue-induced craving," a strong urge to use opioids triggered by environmental cues associated with past usage. Currently, there is no standard device to monitor cue-induced cravings, leaving a vulnerability "blindspot" for clinicians and patients, and precluding objective treatment of cue-induced cravings. Neurotype Inc. is developing NeuromarkR™, a neurofeedback software that works with electroencephalogram (EEG) devices. The software aims to detect and address specific brain biomarkers related to cue-induced craving, offering an objective and targeted approach to treatment.
Methods: In previous and ongoing Small Business Innovation Research (SBIR) projects funded by the National Institute on Drug Abuse, NeuromarkR™'s prototype was tested in a clinical setting. Twenty-one OUD patients from a 28-day residential treatment program participated in at least two NeuromarkR™ assessments. The software analyzed the extent to which Event-Related Potential (ERP) brain responses elicited by opioid cues (e.g., images containing a pill bottle) resemble ERPs elicited by naturally appetitive cues (e.g., palatable foods). This biomarker is associated with dysregulated motivated attention and adverse outcomes, including recurrent drug use.
Results: Patients with OUD who returned to use following residential care exhibited a more prominent ERP biomarker of motivated attention to opioid-related cues relative to their abstaining counterparts.
Conclusions: Through interactions with over 200 stakeholders, including care providers, patients, and regulators, during the NIH Innovation Corps program, FDA pre-submission meetings, and customer discovery interviews, we've gathered key insights about NeuromarkR™. Firstly, it has potential as a clinical decision support tool for prescribing medications and evaluating the effectiveness of new and existing preventative therapies like Cognitive Behavioral Therapy (CBT), mindfulness, and brain stimulation. Secondly, NeuromarkR™ could be instrumental in monitoring and customizing biofeedback therapies, such as closed-loop attention-bias modification, to train the brain to be less responsive to opioid-related cues.
Financial Support: This work was made possible by grants R43DA057773 and R44DA059517 from the National Institute on Drug Abuse.

Relationship Between Venous Blood and Dermal Interstitial Fluid Alcohol Concentration After Heathy Volunteers Consume Alcohol Using a Novel Ambulatory Biosensor

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Drug Category: Alcohol
Topic: Technology (e.g., mHealth), chemistry, pharmacokinetics
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research
Aim: Currently, blood is the gold standard biological fluid for quantitative alcohol concentrations. Blood sampling is invasive and takes a number of hours for results to be quantified. Breath samples offer rapid results and are generally an excellent compartment but are subject to buccal retention soon after consumption leading to erroneously high estimates of BAC. The present study was conducted to develop and test a novel biosensor device that can be worn on the body and provide rapid measures of blood alcohol that is not subject to environmental factors. Four LabPatch-alcohol sensors fit on a 5 x 10 mm cell and capitalize on the fact that alcohol equilibrates with interstitial fluid (ISF) very quickly. ISF differs from sweat in that it is in direct contact with the capillaries in tissue while sweat is a glandular excretion product. During operation, the cells are in contact with the skin and extract ~9 nanoliters of ISF via slight heating (40°C) over a 3-5 second period and process the fluid using an enzymatic reaction; results are available in about 100 - 120 seconds. The cells are not reused.
Methods: A total of 19 male and 8 female healthy paid 21-38 yo volunteers were fitted with vital signs monitoring and a subset with an i.v. catheter for blood withdrawal. Blood was sampled at 5-min intervals and

analyzed for blood alcohol concentration (BAC). All participants also provided breath samples (Alco-Sensor-FSL) and ISF samples from either a finger or shoulder at the same time points as the blood samples were collected. Alcohol concentrations from skin sites were collected at baseline and at 5- to 10-min intervals after consuming between 0.3 and 0.9 g/kg of 40% alcohol. Participants consumed the alcohol in 10 – 15 min and answered a series of VAS questions on their mood state and confidence in being able to drive a motor vehicle at 30 min intervals.
Results: Alcohol was detected on participant's breath immediately after drinking and followed the typical absorption profile. ISF and BAC appeared 10-15 min after drinking onset and paralleled one another through all three major phases of absorption, distribution, and elimination. All three methods revealed similar alcohol concentrations during the distribution and elimination phases with Tmax between 50 – 60 min post drinking onset and Cmax of between 40 – 120 mg/dL after between 0.3 and 0.9 g/kg doses. As expected, the absorption phase of the breath samples was artificially elevated. The correlation coefficients between ISF and breath was 0.812 when the sample was collected from a shoulder; the correlation between ISF and blood was 0.854. Subjective reports of "drunk", "floating", and confidence in driving a car paralleled the changes in alcohol concentration.
Conclusions: This is the first demonstration of a device that collects and analyzes ISF samples for alcohol concentration in under 2 minutes. Based on the results, ISF is an excellent substitute for blood and because it can be collected noninvasively, offers a unique way of monitoring the BAC of individuals in a variety work or social settings as well as in patients who are being treated for alcohol use disorder.
Financial Support: NIAAA Grant grant 1 R43 AA026123

ORAL SESSION: NEW FENTANYL COUNTERMEASURES

Anti-Fentanyl Vaccine Alone and in Combination With Buprenorphine Prevents Distribution and Antinociceptive Effects of Fentanyl

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Drug Category: Opiates/Opioids
Topic: Substance Use Disorder
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research
Aim: Vaccine immunotherapy may address the rising incidence of opioid use disorder (OUD) and overdose deaths from fentanyl (FEN) in patients with OUD for whom current treatments are inadequate. The aim of this study was to determine the antinociception effects of FEN in rats immunized with our adjuvanted anti-FEN conjugate vaccine (FEN-CRM197+dmLT) administered with and without buprenorphine (BUP).
Methods: Male Sprague Dawley rats (N=15/group) were immunized at 0, 3 and 6 weeks and anti-FEN IgG antibody levels determined at 4, 6, 8 and 10 weeks post initial vaccination using ELISA. BUP (1.5 and 3.0mg/kg/day) was administered chronically via surgically implanted osmotic mini-pumps. The antinociception effects of FEN (0.05 and 0.1 mg/kg) were assessed using the tail flick and hot plate assays. Brain FEN concentrations were also determined using ELISA.
Results: Results show significant immunogenicity of our conjugate anti-FEN vaccine administered alone and in combination with BUP. Immunized rats produced significant levels of anti-FEN antibodies that were highly effective against FEN–induced antinociception. Chronic BUP alone attenuated the antinociception effects of FEN in the tail flick and hot plate assays; yet combining the FEN vaccine with BUP attenuated FEN's antinociception effects to a greater extent than BUP alone. Immunization prevented FEN from entering the brain. Finally, brain FEN was highly correlated with IgA levels following FEN administration at twenty weeks post-initial vaccination, but not correlated with serum IgG, IgG1 and IgG2a anti-body isotypes.
Conclusions: These results confirm our previous studies and extend them by combining the anti-FEN vaccine with BUP, the most common current treatment for OUD. We also reveal further evidence for the importance

of the IgA antibody isotype on vaccine efficacy. Thus, clinical development of this vaccine for OUD in combination with current FDA approved treatments like BUP is clearly supported.
Financial Support: Office of the Assistant Secretary of Defense for Health Affairs through the Alcohol and Substance Abuse Research Program under Award No. W81XWH-18-2-0044 to CNH.

First-In-Human Study of the Safety, Tolerability and Pharmacokinetics of CSX-1004, an Investigational Anti-Fentanyl Monoclonal Antibody

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Drug Category: Opiates/Opioids
Topic: Treatment
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research
Aim: CSX-1004 is a novel, investigational anti-fentanyl monoclonal antibody being evaluated for prevention of overdose from fentanyl and fentanyl analogs. The objective of this Phase 1, first-in-human clinical study was to evaluate the safety, tolerability and pharmacokinetics of CSX-1004 in healthy volunteers.
Methods: Using an escalating dose design, eligible subjects were randomly assigned to receive single doses of CSX-1004 intravenous injection (1, 3, 10, or 30 mg/kg) or placebo (sterile saline) on Day 1 in 4 cohorts of 8 subjects each (n=6 CSX-1004; n=2 placebo). Subjects remained in the clinical research site until Day 14 for safety assessments and collection of PK blood samples. Following Day 14 assessments, subjects were released from the clinical research site and returned on Days 21, 28, 42, 56, 84, and 112 for outpatient visits to assess safety and collect PK blood samples. Safety was assessed through evaluation of adverse events (AEs), vital signs, physical examinations, infusion-site reactions, ECGs, and clinical laboratory tests.
Results: Across the first 3 dosing cohorts (n=24 subjects), 14 of 24 (58.3%) were male and mean (SD) age was 33.0 (7.0). A total of 7 adverse events were reported including insomnia, elevated ALT, constipation, paronychia, headache, contact dermatitis, and infusion-site reaction. All AEs resolved and were rated as Grade 1 (mild) and no serious AEs were reported. The pharmacokinetic profile was characterized by a rapid distribution phase (median Tmax: 1 hr) followed by a slower elimination phase with a multi-week half-life. Across the dose range tested, CSX-1004 exposure was generally linear and dose-proportional. Appreciable serum concentrations of CSX-1004 were maintained through at least 28 days.
Conclusions: CSX-1004 was generally well-tolerated with only infrequent and mild AEs. The pharmacokinetic profile is consistent with a once-monthly product that can potentially block or attenuate the toxic effects of fentanyl and fentanyl analogs.
Financial Support: None

Novel Compounds EO-139 and YZ-166 as Potential Countermeasures for Reversing Fentanyl-Induced Antinociception, Motor Incapacitation and Respiratory Depression

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Drug Category: Opiates/Opioids
Topic: Other, Rescue Agents
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research
Aim: Unlike morphine, fentanyl causes vocal cord closure and rigidity of the chest wall muscles, an effect known as “wooden chest syndrome”, and this effect may not be fully reversed by pure mu opioid receptor (MOR) antagonists such as naloxone or naltrexone. This study assessed the ability of two novel compounds (EO-139 and YZ-166) to serve as MOR antagonists in reversing fentanyl-induced antinociception, locomotor incapacitation and respiratory depression.

Methods: For antinociception, male and female F1 hybrid mice (n=31) were administered fentanyl (1 mg/kg; s.c.), followed by either EO-139 or YZ-166 using a cumulative dosing procedure, with nociception measured by latency to paw lick on a hot plate. For locomotion and respiration, male and female Sprague-Dawley rats (n=43) were administered saline or fentanyl (200 µg/kg; s.c.) 15 min prior to a second injection of one of the following: (1) vehicle, (2) EO-139 (0.0003–0.1 mg/kg; s.c.), or (3) YZ-166 (0.003-1 mg/kg; s.c.). Rats were immediately placed into a locomotor chamber for 15 min, followed by placement into a plethysmography chamber to record ventilatory effort for 30 minutes.
Results: As expected, with the hot plate assay, both EO-139 and YZ-166 dose-dependently reversed fentanyl-induced antinociception. Unlike YZ-166, EO-139 yielded notable sex differences in the dose required to produce 50% reversal (AD50). EO-139 and YZ-166 also reversed the respiratory depressant effects of fentanyl ($F(6,59)=5.613$, $p=0.0001$; $F(7,98)=11.88$, $p<0.0001$), but not fentanyl-induced locomotor depression within the dose ranges tested ($F(6,58)=0.8326$, $p=0.5497$; $F(7,98)=1.709$, $p=0.1157$). Most notable, unlike EO-139, YZ-166 not only reversed fentanyl-induced respiratory depression, it stimulated respiration above baseline control following the fentanyl attack, suggesting "supra-antagonism".
Conclusions: This study provides evidence that EO-139 and YZ-166 attenuate opioid-induced antinociception and respiratory depression. Moreover, YZ-166 has a profile on respiratory depression that may offer a superior countermeasure agent against exposure to high-potency synthetic opioids.
Financial Support: U01 DA051377 and KY-WV LSAMP

A Next-Generation Nanoparticles (NP)-Based Anti-Opioid Vaccine: Pre-Clinical Efficacy With a Focus on Innate Immunity Response

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Drug Category: Opiates/Opioids
Topic: Substance Use Disorder, Vaccines
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research
Aim: The ongoing opioid use disorder (OUD) and overdose epidemic has already claimed millions of lives since 1999, with almost 2.7 million people currently diagnosed with OUD. Moreover, fatal overdoses continue to surpass 100,000 incidents annually. Saving lives and counteracting the effects of such a public health crisis and economic burden require accelerating the translation of innovative, effective, and safe treatments to augment existing measures. To address this challenge, our team is advancing vaccines against a variety of opioids as a preventative as well as therapeutic strategy against OUD and overdose. Therefore, we explored the formulation of a lead oxycodone vaccine into a novel lipid hybrid nanoparticle (LPNP) platform and tested it in mice for protection against oxycodone-induced pharmacological effects.
Methods: To investigate the efficacy of LPNP platform in the context of conjugate vaccines against oxycodone and fentanyl, male Sprague Dawley (n=8) rats were immunized with either conjugate vaccine or LPNP-based vaccine on days 0, 21, and 42, and bled on day 49 to measure immunogenicity using ELISA. Rats were challenged with fentanyl and oxycodone and tested for drug-induced antinociception, respiratory and cardiovascular depression and drug blood-brain distribution. To decipher innate immunity mechanisms associated with this nanocarrier, the activation and maturation of macrophage and dendritic cell (DC) lines incubated with vaccines were assessed via flowcytometry. Statistical analyses included ANOVA and post-hoc test as appropriate.
Results: We revealed that the LPNP-formulated vaccines are more effective in inducing macrophages activation marker (iNOS) and DCs co-stimulatory molecules and maturation markers (CD86, CD40, and MHC II) compared to the conventional conjugate vaccines.
Conclusions: LPNP can be used to formulate vaccines against OUD and their immunological mechanisms can provide insights into significant cellular and molecular vaccine targets. Studies are ongoing to dissect the innate antigen presenting cells (APC) dynamics upon vaccination in mice to identify key APCs subsets contributing to efficacy.
Financial Support: This work was supported by the NIH under UG3/UH3 DA048775 award.

ORAL SESSION: THE PRESSURE'S ON: CARDIOVASCULAR OUTCOMES IN SUDS

Influence of Cocaine Use Reduction on Cardiovascular Biomarkers

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Drug Category: Stimulants
Topic: Comorbidities
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research

Aim: Reducing problem behaviors is common in medical practice wherein at-risk individuals are counseled to make moderate, sustainable changes in lifestyle, yet for most substance use disorders, complete abstinence is the only accepted treatment endpoint. Limited prospective research has evaluated health benefits produced by reduced drug use. This study sought to determine how reduced cocaine use impacted biomarkers of cardiovascular health. We hypothesized that reduced cocaine use would translate to improvement on these biomarkers.
Methods: Treatment seeking participants with Cocaine Use Disorder (N=127) were enrolled in a 12-week clinical trial that used contingency management to reduce cocaine use. Participants were randomly assigned 1:1:1 to High Value Reinforcers for cocaine abstinence (n=44), Low Value Reinforcers for cocaine abstinence (n=41) or Non-Contingent Control (n=42). At baseline and 6-week intervals during the trial, blood was drawn and assayed using ELISA for biomarkers of cardiovascular health (i.e., endothelin-1, stromal cell derived factor-1a [SDF1a], soluble intercellular adhesion molecule-1 [SICAM1], soluble CD40L and neutrophil activating peptide-2). Time- and group-varying weekly percent of benzoylecgonine-negative urine samples was analyzed as the primary predictor of these biomarkers using generalized linear mixed models (GLMM).
Results: GLMM revealed that reductions in cocaine use reduced SDF1a and increased SICAM1 levels ($p > 0.05$) in the active treatment groups.
Conclusions: Reduced cocaine use primarily affected markers of endothelial function (i.e., SDF1a and SICAM1). Greater reductions translated to reduced levels of SDF1a, an indicator of cardiovascular health and organ injury, but increased levels of SICAM1, an indicator of inflammatory processes and plaque formation. Prior research has shown that these biomarkers may have a reciprocal relationship. Further analyses are needed to understand the impact of these changes on long term cardiovascular health and function.
Financial Support: R01 DA 043938, T32 DA 035200, TL1 TR 001997, UL1 TR 001998

History of Cardiovascular Health Problems among Decedents of Fatal Stimulant Poisoning, a Preliminary Analysis of a Psychological Autopsy Study

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Drug Category: Stimulants
Topic: Prevention
Abstract Detail: Other
Abstract Category: Original Research

Aim: Despite recent increases in deaths attributed to acute stimulant (i.e., cocaine and methamphetamine) poisoning, little is known about the nature of these deaths. The LASSO study aims to identify behavioral, clinical, and psychological antecedents of these deaths. We hypothesized that most decedents would have cardiovascular problems.

Methods: The LASSO study is collecting detailed ante-mortem data for 101 decedents of acute stimulant poisoning in San Francisco, CA (70 without opioid involvement, 31 involving fentanyl). Data sources include mixed-method interviews with close contacts of decedents, state death records, medical examiner reports (e.g., autopsy, toxicology), and electronic medical records. For this preliminary analysis, we used state death records for sociodemographic characteristics and informant interviews for cardiovascular history. Proportions were compared using Pearson chi-square tests with Fisher's exact tests for expected cell counts>5. A p-value of>0.05 was considered significant.
Results: Of 93 decedents with current complete data, median age was 58 (IQR: 47-61), 77% were male, 37% were White and 31% Black/African American. Among 65 decedents with cardiac data from informant interviews, most had a cardiovascular problem (58%), with a significantly higher prevalence among stimulant-no-opioid compared to stimulant-fentanyl decedents (67% vs 41%, p=0.04). Of the 56 decedents with past-year cardiac symptom data (i.e., chest pain or rapid heartbeat), 61% had at least one symptom (67% among stimulant-no-opioid and 50% among stimulant-fentanyl decedents, p=0.22).
Conclusions: We found a high prevalence of prior cardiovascular health problems among decedents of acute stimulant poisoning, with a significantly higher proportion among stimulant-no-opioid compared to stimulant-fentanyl deaths. We will also present additional cardiovascular health data that will be available in early 2024 from medical examiner investigations and medical records for the complete cohort of 101 decedents.
Financial Support: CDC grant CE003364

Characterizing Cardiovascular Health Among Individuals With Opioid Use Disorder

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Drug Category: Opiates/Opioids
Topic: Substance Use Disorder, Cardiovascular Health
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research
Aim: Cardiovascular diseases are the leading cause of mortality in the United States and Opioid use disorder (OUD) affects an estimated 2.7 million people. The prevalence and risk of cardiovascular diseases among individuals with OUD is not well understood. The aim of this exploratory study was to characterize cardiovascular health among individuals with OUD.
Methods: Demographic, health, and substance use data for this secondary analysis were collected as part of research screening procedures from individuals with OUD at Columbia University Irving Medical Center, via semi-structured interviews. Cardiovascular health assessments included measures of heart rate, blood pressure (BP), ECG, and self-reported history of cardiovascular and other chronic diseases (e.g., diabetes, HIV, chronic kidney disease).
Results: The final sample consisted of 31 males and 9 females with an average age of 43.7 years (±11.1). Ninety percent reported heroin as their drug of choice. The most common routes of opioid administration reported were intranasally (62.5%) and intravenous (50%). Average duration of illicit opioid use was 14.3 (±13.1) years. Average heart rate was 74 beats per minute (±17). Thirty-five percent of participants had high (systolic: 120–129 mmHg, diastolic:>80 mmHg) and 12.5% elevated BP (systolic: ≥130 mmHg, diastolic: ≥80 mmHg). However, only 2.5% of participants self-reported having a diagnosis of high BP and/or currently receiving treatment for high BP. Approximately 57% of participants' ECGs were flagged as abnormal (i.e., deviating from normal heart rhythm, rate, and/or electrical pattern), and in 20% deviations from a normal sinus rhythm were detected.
Conclusions: Given the high rates of ECG and sinus rhythm abnormalities detected in this sample, an increased focus on the cardiovascular health of people with OUD is warranted. Future studies should investigate cardiovascular functioning among individuals with OUD more comprehensively to better understand how chronic opioid use may impact cardiovascular health and identify opportunities for intervention.
Financial Support: Research partially supported by National Institute on Drug Abuse award R25DA035161.

Comparison of Cardiopulmonary Effects of Cigarettes and E-Cigarettes in Individuals with Chronic Obstructive Pulmonary Disease (COPD)

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Drug Category: Nicotine/Tobacco
Topic: Harm Reduction
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research

Aim: E-cigarettes may be less harmful than combustible cigarettes, though results from research with objective outcomes are limited. Effects of combustible versus e-cigarettes in individuals with chronic obstructive pulmonary disease (COPD) were compared, and a contingency management program reinforcing combustible-cigarette abstinence was evaluated.
Methods: Twenty-one individuals at least 40 years old who smoke (≥5 cigarettes/day for ≥1 year) while diagnosed with COPD underwent two consecutive randomly ordered 2-week phases: a cigarette phase (usual-brand cigarettes) and nicotine-containing e-cigarette phase (combustible-cigarette abstinence with 3% and/or 5% nicotine tobacco-flavored JUUL available). During the e-cigarette phase, participants earned monetary incentives for CO readings ≤6ppm to promote cigarette abstinence. Pulmonary (spirometry, oscillometry, COPD Assessment Test [CAT], Saint George's Respiratory Questionnaire for COPD [SGRQ-C]) and cardiac (heart rate, blood pressure) assessments were completed at baseline and after each phase. Changes in pulmonary and cardiac measures across assessments were analyzed using a one-way ANOVA.
Results: Fourteen participants abstained from cigarettes during the e-cigarette phase, and changes in their dependent measures across phases were assessed. Changes in objective (spirometry, oscillometry) and self-reported (CAT, SGRQ-C) pulmonary measures were minor and did not meet thresholds for statistical significance. Diastolic blood pressure, the only cardiac measure that significantly changed across phases ($F(2,41) = 3.54$, $p = 0.038$), was lower after the e-cigarette phase than after the cigarette phase ($p = 0.03$).
Conclusions: Changes in cardiac and pulmonary functioning were minimal, and the contingency management program largely maintained cigarette abstinence. Some participants anecdotally reported improved pulmonary health following e-cigarette use, but changes in average CAT and total SGRQ-C scores were negligible. However, the absence of impairments in pulmonary and cardiac health during the e-cigarette phase is promising. Evaluations of longer durations of e-cigarette exposure, with concurrent cigarette abstinence, are warranted to determine the safety of e-cigarettes as a potential replacement for combustible-cigarettes.
Financial Support: Tobacco Centers of Regulatory Science (TCORS) Award U54DA036114 from the National Institute on Drug Abuse (NIDA) and Food and Drug Administration (FDA). Content is solely the authors' responsibility and does not necessarily represent the official views of these institutions.

ORAL SESSION: THE FAST LANE FORWARD: EXPLORING NOVEL STIMULANT TREATMENTS

Barriers and Facilitators to Integrate Methamphetamine Use Interventions into Methadone treatment: Patients and Providers' Perspectives

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Drug Category: Stimulants
Topic: Treatment
Abstract Detail: Clinical - Experimental

Abstract Category: Original Research
Aim: Rising methamphetamine use is threatening the achievements of HIV treatment and prevention programs. Integration of methamphetamine intervention into methadone treatment is recommended to improve drug treatment outcomes. We explored the barriers and facilitators for integrating methamphetamine use interventions into methadone treatment settings.
Methods: Within the STAR-OM trial (R01 DA050486), we conducted 144 in-depth interviews at pre- and post-intervention (41 participants and 42 providers) in 15 methadone clinics in Northern and Southern Vietnam. We developed the interview guides following the Consolidated Framework for Implementation Research and conducted deductive and inductive coding with the transcripts.
Results: Facilitators: Evidence-based interventions for methamphetamine use were considered highly feasible to be integrated into methadone settings in terms of staff structure and program infrastructure. Both participants and providers perceived positive impact on provider-participant relationship and participants' outcomes at post-intervention. The recent creation of a department for addiction treatment that houses methadone clinics in all district health centers was favorable to the integration of methamphetamine intervention into methadone programs.
Barriers: the barriers to implement methamphetamine interventions overlapped with the existing challenges of methadone programs including staff shortage and turnover and no budget to purchase drug tests. The lack of indicators to track providers' performance in methamphetamine use intervention did not motivate them to provide such additional tasks. Some evidence-based interventions, such as contingency management, might go against some providers' ideology and usual treatment practice. For participants with jobs, participation in group work could be challenging.
Conclusions: Integration of methamphetamine use intervention into methadone treatment is feasible and acceptable. Yet, major existing obstacles require significant strategies to translate methamphetamine intervention policy into concrete implementation guidelines, ensure adequate staff-to-participant ratio and tailor interventions to participants with different living conditions.
Financial Support: R01 DA050486

Efficacy and Safety of Modafinil for Treatment of Amphetamine-Type Stimulant Use Disorder: A Systematic Review and Meta-Analysis of Randomized Placebo-Controlled Trials

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Drug Category: Stimulants
Topic: Treatment
Abstract Detail: Clinical - Experimental
Abstract Category: Literature Review
Aim: This systematic review and meta-analysis aimed to evaluate the efficacy and safety of modafinil for the treatment of amphetamine-type stimulants (ATS) use disorder (ATSUD).
Methods (Optional): A comprehensive search of major indexing sources and trial registries was conducted on February 15th, 2023. Eligible studies were randomized placebo-controlled trials (RCT) of modafinil in individuals meeting the criteria for the DSM-IV, DSM-IV-TR, and DSM-5 of ATSUD. Eligible studies were assessed for risk of bias, using the Risk of Bias Assessment tool (RoB 2). Outcomes included the effect of modafinil on ATS use by urinalysis, retention in treatment, ATS craving, dropouts due to adverse events (AE), and serious AE. Subgroup analysis by modafinil dose was conducted. Risk ratio (RR) or Peto's odds ratio (OR) were calculated for the random-effect meta-analysis of dichotomous variables and standardized mean difference (SMD) was calculated for the random-effect meta-analysis of continuous variables.
Results (Optional): Five RCTs (n= 451 participants) were included. Modafinil did not significantly impact ATS use (RR= 0.99; 95%CI= 0.97–1.02; p= 0.655), retention in treatment (RR= 1.02; 95%CI= 0.91–1.14; p= 0.799), or ATS craving (SMD= -0.343; 95%CI= -1.19–0.50; p= 0.414). No significant effect on dropouts due to AEs was observed (Peto's OR= 0.47; 95%CI= 0.17–1.34; p= 0.158). These results were consistent across

subgroup analyses by modafinil dose. However, more serious AEs were reported in the modafinil group, particularly at higher doses (Peto's OR= 4.80; 95%CI= 1.18–19.57; p= 0.029).
Conclusions: While the current evidence remains limited, modafinil is not a suitable pharmacological intervention for ATSUD. These results strengthen the call for continued research into other potentially effective treatments and harm reduction strategies for ATSUD.
Financial Support: This meta-analysis was supported by the Canadian Institutes of Health Research (CIHR) (grant number REN-181675), Université de Montréal and Centre de recherche du Centre hospitalier de l'Université de Montréal (CRCHUM).

Racial and Ethnic Differences in Patients Reported Outcomes Among Participants in a Randomized Controlled Trial of Extended-Release Naltrexone and Bupropion for Methamphetamine Use Disorder

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Drug Category: Stimulants
Topic: Treatment
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research
Aim: The aim of this secondary analysis was to explore racial and ethnic differences in baseline sociodemographic and clinical characteristics as well as treatment effects on a measure of substance use recovery, depression symptoms, and methamphetamine craving among participants in a pharmacotherapy trial for methamphetamine use disorder
Methods: The ADAPT-2 trial was a multisite, 12-week randomized, double-blind, trial that employed a two-stage sequential parallel design to evaluate the efficacy of combination naltrexone (NTX) and oral bupropion (BUP) vs. placebo for Meth UD. Treatment effect was calculated as the weighted mean change in outcomes in the NTX-BUP minus placebo group across the two stages of treatment.
Results: Of the 403 participants in the ADAPT-2 trial, the majority (65%) reported non-Hispanic White, while 14%, 11% and 10% reported Hispanic, non-Hispanic Black, and non-Hispanic other racial and ethnic categories respectively. At baseline non-Hispanic Black participants reported less severe indicators of methamphetamine use than non-Hispanic White. Treatment effects for recovery, depression symptoms and methamphetamine cravings did not significantly differ by race and ethnicity.
Conclusions: Although we found racial and ethnic differences at baseline, our findings did not show racial and ethnic differences in treatment effects of NTX-BUP on recovery, depression symptoms and methamphetamine cravings. However, our findings also highlight the need to expand representation of racial and ethnic minority groups in future trials.
Financial Support: NIDA (grant# K01DA047918)

Low-Barrier Long-Acting Injectable Antiretrovirals for HIV Treatment and Prevention Among People Who Use Drugs

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Drug Category: Stimulants
Topic: Infectious Disease (e.g., HIV, HCV)
Abstract Detail: Clinical - Experimental
Abstract Category: Program Descriptions
Aim: Long-acting (LA) antiretrovirals—including intramuscular (IM) cabotegravir (CAB), IM rilpivirine (RPV), and subcutaneous (SQ) lenacapavir (LEN)—may provide meaningful benefit to people who use drugs (PWUD) and people experiencing homelessness (PEH), who face barriers in adhering to daily oral HIV

antiretroviral therapy (ART) or pre-exposure prophylaxis (PrEP). However, their use has not been studied in this population. We aimed to evaluate the feasibility of LA antiretrovirals in a clinic designated for PEH.
Methods (Optional): A multidisciplinary care model with robust monitoring and outreach support was developed to provide LA-ART and LA-PrEP to eligible patients at a low-barrier, community-based clinic designated for PWUD and PEH in San Francisco. The protocol featured exclusive use of a direct-to-inject approach, facilitation of drop-in visits 6 days per week, and enhanced follow-up and tracking support. It lacked requirements for baseline HIV viral suppression prior to initiating LA-ART. Rates of HIV viremia and on-time injections were evaluated over the program's first two years of implementation.
Results (Optional): Between November 2021-2023, 33 patients initiated LA-ART or LA-PrEP (median age, 37 years; 27% transgender/non-binary; 73% non-White; 27% street homeless; 45% sheltered homeless; 30% with opioid use disorder; 82% with methamphetamine use disorder). Among 18 patients with HIV, 14 initiated LA-ART with detectable viremia (median CD4 count, 340 cells/mm3; mean log10 viral load, 3.53; standard deviation [SD], 1.62), 8 had never previously been virally suppressed, and all but 1 achieved and maintained viral suppression (mean, 9.67 months; SD, 8.30). Among 15 patients started on LA-PrEP, all remained HIV-negative (mean, 4.73 months; SD, 2.89). Of 224 injections administered in total, 8% were delayed< 7 days.
Conclusions: The implementation of LA antiretrovirals is feasible within low-barrier, highly supportive settings that serve PWUD. While longer-term follow-up studies are necessary, the effective scale-up of such programs may be critical in addressing HIV disparities among PWUD and PEH.
Financial Support: None

ORAL SESSION: DOPE DENDRITES: CANNABIS AND THE NERVOUS SYSTEM

Subjective Euphoric Response to Delta-9-Tetrahydrocannabinol (THC) is Associated With Neural Reward Anticipation During THC Intoxication

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Drug Category: Cannabis/Cannabinoids
Topic: Neurobiology/Neuroscience
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research
Aim: Sensitivity to the rewarding properties of drugs is an established risk factor for continued drug use and development of substance use disorders (SUDs). Notably, greater subjective response to drugs, particularly drug-induced euphoria, has been linked to continued use and development of SUD. However, it is unclear if this is true for cannabis. The present study aimed to investigate the relationship between subjective euphoria and neural reward during THC intoxication among young adult cannabis users. We hypothesized that greater euphoric response to THC would be related to more neural activation to anticipation of monetary reward during THC intoxication.
Methods: Fifteen young adult cannabis users with no lifetime history of cannabis use disorder (CUD) participated in a within-subjects, randomized, double-blind, placebo-controlled study. Participants provided self-report measures of euphoria at regular intervals and completed the Monetary Incentive Delay (MID) task during functional magnetic resonance imaging (fMRI), approximately 120 minutes after ingesting placebo or 7.5 mg oral THC (dronabinol). Regression analyses examined the relationship between subjective euphoria and neural reward anticipation using a priori anatomical regions-of-interest (nucleus accumbens [NAcc], caudate, putamen).
Results: Greater euphoric response to THC was related to more reward anticipation activation during THC intoxication in the NAcc (β=.59, p=.02) and putamen (β=.62, p=.01), but not the caudate (β=.37, p=.18). Subjective euphoria and neural reward anticipation were not related to lifetime or past-month cannabis use frequency.
Conclusions: The association between greater euphoria and heightened striatal reward anticipation during THC intoxication provides valuable insights into the neural mechanisms underlying subjective effects of THC.

These results enhance our understanding of the neural basis of cannabis-related experiences and provide additional support that like other drugs, subjective euphoric response to THC may be a risk factor for continued use and CUD. Ongoing and future studies with larger sample sizes are needed to replicate this finding.
Financial Support: K23DA048132

Mobile EEG is Sensitive to Chronic Cannabis Use Between Individuals, but not Acute Anxiety Within Individuals

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Drug Category: Cannabis/Cannabinoids
Topic: Imaging
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research
Aim: Chronic cannabis use is associated with alterations in brain structure and function. Electroencephalography (EEG) is one measure sensitive to these alterations. Mobile EEG is a novel innovation enabling large-scale EEG assessments. We aimed to determine whether mobile EEG (Muse S, Interaxon) is sensitive to chronic cannabis use or acute anxiety in people who use cannabis regularly.
Methods: Muse S recorded EEG power (average of delta, theta, beta, alpha, and gamma) during 5 minutes of rest (N = 100 healthy volunteers; N = 50 males, N = 50 females; Age: 29 ± 8; Average days of cannabis use per year: 152 ± 226) or during the Cold Pressor Test (CPT; N = 36 healthy volunteers; N = 18 males, N = 18 females; Age: 32 ± 9; Average days of cannabis use per year: 141 ± 110). The CPT is an acute pain and stress test consisting of warm and cold-water conditions. The State Anxiety Inventory (SAI) was completed immediately following the CPT.
Results: At rest, EEG power was positively associated with average days of cannabis use per year (N = 100; R = 0.30, p = 0.006), but not in the female volunteers alone (N = 50; R = 0.17, p = 0.213). The association was therefore stronger in males alone (N = 50; R = 0.56, p> 0.001). Males and females did not differ in cannabis use. During the CPT, cold water induced greater SAI scores than warm (p> 0.001), however no differences in EEG power were detected between the water temperature conditions.
Conclusions: Greater cannabis use between individuals was associated with greater EEG power, whereas within individuals, EEG power was not affected by state anxiety. These findings suggest EEG power may be more sensitive as a marker of chronic cannabis use than state anxiety.
Financial Support: R01DA057252 and R01DA047296

Neurochemical and Behavioral Effects of Cannabinoid CB1 Agonist in Male Mice

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Drug Category: Cannabis/Cannabinoids
Topic: Behavioral Pharmacology
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research
Aim: To date, it has not been fully elucidated how cannabinoid-induced changes in neurochemical dynamics in the nucleus accumbens shell impacts reward-related behavior. Here, we aim to investigate the relationship between these two outcomes of cannabinoid agonist exposure using both partial and full cannabinoid agonists.
Methods: Here, we first utilized in vivo microdialysis and liquid chromatography-mass spectrometry to quantify the effects of Δ9-THC (0.1–3.2 mg/kg), the synthetic partial CB1 agonists AM11101 (0.1–3.2 mg/kg), and the full CB1 agonist AM8936 (0.01–1.0 mg/kg) on extracellular levels of dopamine (DA), glutamate (Glu) and GABA within the nAcc shell of mice (n=6-8 per group). Next, using conditioned place preference (CPP), we determined the relationship between Δ9-THC (0.1–1.0 mg/kg), AM11101 (0.1–1.0

mg/kg), and AM8936 (0.01–0.1 mg/kg) induced rewarding properties and changes in DA, GABA, and Glu levels (n=12-16 per group).
Results: Results show that lower doses of all three cannabinoids (0.32 mg/kg Δ9-THC and AM11101, 0.032 mg/kg AM8936) increase DA in the nAcc shell to 134–161% basal values, whereas administration of higher doses (0.1–1.0 mg/kg AM8936, 1.0–3.2 mg/kg AM11101 and Δ9-THC) decrease DA levels to 59-70% basal values. Notably, the onset of these DA changes is immediate (i.e., 20 min) for Δ9-THC and AM11101 but delayed by about 140 minutes after AM8936 administration. Interestingly, during the same time period, the doses of Δ9-THC and AM8936 that increased DA also elevated GABA to 219% and 157% of basal values, as well as Glu to 133% and 136% of basal values (respectively). In contrast, the low doses of AM11101 that increase DA have little effect on GABA and Glu. Δ9-THC produces no change in Glu or GABA at doses that decrease DA. However, high doses of AM11101 and AM8936 both decrease GABA to 54% and 58% basal values, as well as Glu to 70% and 73% basal values (respectively). Results from CPP studies demonstrate that Δ9-THC (0.1–0.32 mg/kg) and AM8936 (0.032 mg/kg) produce increases in preference score, whereas AM11101 (0.1–1.0 mg/kg) did not induced CPP. Correlation analysis of grouped data from all CB1 drugs revealed a strong positive relationship between increases in DA, GABA, and Glu in the nAcc shell and rewarding properties of Δ9-THC, AM11101, and AM8936.
Conclusions: Together, these data show a biphasic dose-response function on DA in the nAcc shell, but the effects on GABA and Glu are distinct among the three CB1 drugs. When considering the CPP data, these findings point to a complex neurochemical dynamic where elevations in DA, GABA, and Glu may all contribute to the rewarding effects from CB1 agonists.
Financial Support: Research supported by T32 grant under Alexandros Makriyannis

Network Topology and Cannabis Use Following two Weeks of Monitored Abstinence: Moderation of Sex and Severity of Use Findings

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Drug Category: Cannabis/Cannabinoids
Topic: Imaging
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research
Aim: Chronic cannabis use (CU) can result in impacts to cognitive performance associated with distributed alterations in neural functioning. However, these alterations are not well-characterized following monitored abstinence. Here, we evaluate differences in functional brain network activity associated with CU in adolescents/young adults.
Methods: Functional connectomes were generated using resting-state fMRI data collected from 79 healthy young adults (41 male) following a monitored period of cannabis abstinence. Network topology metrics were calculated for each of the 7 Yeo 2011 intrinsic connectivity networks (ICNs) and on the whole-brain level. (1) Multiple linear regressions were used to evaluate whether CU (heavy-users, n=27 vs non-using controls, n=37) was associated with network topology metric differences after controlling for past-year alcohol use, age, sex, and cotinine levels. (2) Regressions were run within CU group to test for associations between cannabis use characteristics (lifetime CU, age of CU initiation, and past year CU) and network topology. (3) Finally, a network-based statistic (NBS) approach was used to search for connectome subcomponents associated with CU groups and characteristics.
Results: No significant association between CU groups and ICN topology was observed. Within male cannabis users, higher past-year CU was associated with significantly higher frontoparietal and ventral attention network (VAN) efficiency and VAN connectivity strength. NBS analyses indicated that connectivity strength within a subnetwork of connections distributed throughout the connectome were significantly associated with past year CU ($p = .046$).
Conclusions: The present findings suggest that differences in resting-state network topology associated with CU may persist after an extended period of abstinence in young adult males, especially those with heavier past year use. While further replication is required in larger samples, these findings suggest potential neuroimaging correlates underlying long-term changes in cognitive performance associated with CU.

Financial Support: This research was supported by the National Institute on Drug Abuse (NIDA) award R01DA030354 and the National Institute of Health (NIH) award U01DA041025 (PI: Lisdahl, K. M.).

ORAL SESSION: DRUG CHOICE: PATHOLOGY IN DECISION MAKING

Subjective Drug-Effect Ratings as Predictors of Cannabis Self-Administration in People Self-Reporting Daily/Near-Daily Cannabis Use

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Drug Category: Cannabis/Cannabinoids
Topic: Behavioral Pharmacology
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research

Aim: Subjective-effects questionnaires and self-administration procedures are key methods for assessing the rewarding effects of drugs, including cannabis. Although positive subjective effects of drugs are thought to promote continued use and are recommended in FDA abuse potential assessments, this relationship has not been well established for cannabis. This analysis determined whether the subjective response to experimenter-administered cannabis predicted cannabis self-administration in people reporting daily/near-daily cannabis use.

Methods: Participant (N=36) data from three prior double-blind, within-subject human laboratory experiments were combined. Subjective effects data were maximum responses on a visual analog scale (0-100) from nine questionnaire items with positive valence. Cannabis self-administration data were the number of smoked cannabis (5.9% THC) or placebo choices made when available as an alternative to a monetary option on concurrent, independent progressive-ratio (n=24) or fixed-ratio (n=12) schedules. The association between subjective effects questionnaire items and drug choices was determined using Pearson's correlations. Questionnaire items with high multicollinearity were excluded from modeling based on Variance Inflation Factor (VIF). Next, a linear mixed-effects model determined which subjective effect, or combination of effects, best predicted cannabis self-administration.

Results: Eight questionnaire items were significantly associated with drug choices. Any Effect, High, and Like Drug had VIFs greater than 10 and were excluded from subsequent analyses. Good Effect, Stimulated, Take Again, Willing to Pay For, and Stoned were included in the linear mixed-effects model as fixed effects and Subject as a random effect. Only Take Again showed evidence of being predictive of cannabis self-administration ($b=0.0541$, $t(31)=1.98$, $p=.057$).

Conclusions: Take Again was the only subjective effect which appeared to predict future cannabis choices in the present sample. These results suggest that subjective ratings of Take Again might serve as a proxy for drug self-administration procedures in the early stages of development for cannabis use disorder interventions.

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Neural Encoding of Subjective Value During Choices for Cocaine Vs. Non-Drug Reinforcers in People who Smoke Cocaine

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Drug Category: Stimulants
Topic: Neurobiology/Neuroscience
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research

Aim: Little is known about the neural mechanisms underpinning drug-related choices in humans. Choices for other reinforcers in healthy populations are guided by subjective values (SV; how individuals value a given reinforcer) encoded in a valuation network including ventromedial prefrontal cortex (vmPFC), nucleus accumbens (NAcc), and dorsal posterior cingulate (dPCC). We investigated neural encoding of SV for smoked cocaine (COC) compared to a non-drug reinforcer, i.e. palatable snack food, in people who smoke cocaine. We hypothesized that: (1) SV signals for both COC and snack would be encoded in the canonical valuation network; and that (2) SV signals for COC would be stronger than SV signals for snacks.
Methods: Non-treatment-seeking, COC smokers (n=9; at least 2 uses of COC/month) completed a within-subject protocol involving 2 counter-balanced fMRI tasks with: (1) COC vs. money choices; and (2) snack vs. money choices. The SV signal was operationalized as the neural correlates of the strength of preference for cannabis/snack choices on a 5-point scale, using parametric modulation. This was done for 3 ROIs (vmPFC; NAcc; dPCC) with FDR small-volume correction.
Results: Positive SV signals for COC, but not snacks, were observed in vmPFC, NAcc, and dPCC. SV encoding in all three ROIs was stronger for COC than for snack foods.
Conclusions: Findings replicate our earlier report of expected neural valuation for cannabis but not snacks in near-daily smokers of cannabis. Results provide preliminary support for models identifying dysregulated neural valuation of non-drug rewards as a hallmark of problematic drug use. Elucidating the relative SV for drug vs. non-drug reinforcers may advance interventions such as contingency management which require the individual to be sufficiently motivated by non-drug rewards in order to shift their drug use behavior.
Financial Support: Research was funded by NIDA (DA034877). TKR effort funded by NIDA (DA050691).

Behavioral Economic Modeling of Incentivized and Hypothetical Valuation: Implications for Pharmacological Study

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Drug Category: Other, Methodology
Topic: Behavioral Economics
Abstract Detail: Other
Abstract Category: Original Research

Aim: Behavioral economic pharmacological evaluations often record respondent behavior via self-reported or "hypothetical" response formats. That is, as a workaround to measure typically complex-to-observe behavior (i.e., substance use), these tasks prompt respondents to report imagined commodity engagement bounded by experimenter-controlled simulated constraints. The association between self-report and observed self-administration has not been extensively examined, lending to an uncertain predictive validity of hypothetical procedures particularly when applied in novel scenarios. The purpose of this analysis was to evaluate the association between an incentivized and hypothetical behavioral economic demand task collected in a human laboratory study of reduced nicotine cigarette expectancies.
Methods: Participants who smoke daily (N=21; 42.9% female) completed four experimental sessions manipulating expectancy (label of "average" nicotine versus "very low" nicotine) and nicotine dose (15.8 mg/g versus 0.4 mg/g). Cigarette use motivation and behavioral economic demand was collected using an incentivized purchase task in which responses were reinforced with purchased cigarette deducted from an experimental income. A hypothetical purchase task relying on verbal behavior manipulations was also collected. Demand data were evaluated using non-linear modelling and the exponentiated demand equation.
Results: Nicotine dose manipulation produced expected physiological effects. Reduced nicotine dose and expectation manipulations each reduced perceived nicotine content, p values> .05. Analysis of incentivized and hypothetical outcomes showed a close correspondence for measures including demand intensity ($r = .56$, $p > .001$) and Pmax ($r = .56$, $p > .001$). Results did not differ based on experimental condition, supporting the validity of hypothetical data collection across varied pharmacological contexts.
Conclusions: These data broadly support the use of hypothetical arrangements for providing close correspondence to more time-intensive and challenging self-administration procedures. Implementation should ultimately consider the balance of ethical, practical, and logistical restrictions when selecting motivation and demand-related endpoints in human behavioral pharmacological studies.

Financial Support: Support was provided by the National Institute on Drug Abuse (NIDA) of the National Institutes of Health (R03 DA054098; T32 DA07209).

Mood and Difficulty Discontinuing Chronic Hypnotic Use

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Drug Category: Benzodiazepines/Sedatives
Topic: Behavioral Pharmacology
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research
Aim: The inability to discontinue hypnotics after chronic use remains a concern, which has never been directly tested in a controlled, blinded, prospective study using self-administration choice procedures. This study reports on measures of mood and difficulty discontinuing hypnotic use in a clinical trial in which persons with insomnia were instructed to stop taking their study medication after 6 months of nightly use.
Methods: DSM-V diagnosed insomnia participants, aged 23-61 years, (n=41, 36 females), with no other sleep disorders, unstable medical or psychiatric diseases or drug dependency completed the trial. Following a screening NPSG participants were randomized to zolpidem XR (12.5 mg), eszopiclone (3 mg), or placebo nightly for 6 months. After 6 months nightly use, over a 2-week discontinuation, they were instructed to discontinue their hypnotic use, but if necessary, to self-administer either 1, 2, or 3 capsules, each packaged separately in labeled envelopes, of their assigned "blinded" medication (zolpidem XR 6.25 mg, 6.25 mg, placebo; eszopiclone 2 mg, 1 mg, placebo as capsules 1, 2 and 3 respectively; or 3 placebos). The BDI II. BAI, ISI, ESS, and POMS were completed at study entry, month6, and study end.
Results: Over the 14 nights 21 participants took zero (51%) capsules and among the 20 taking capsules (SAer) the median total number chosen was 3. BDI II scores at study entry were significantly higher (6.3 +/-2.4) in the SAer group compared to the non-SAer (3.2 +/- 0.8) group ($p<0.05$). SA groups did not differ in BAI, ISI, or ESS scores. At study end both BDI II ($p<0.001$) and BAI ($p<0.05$) scores had declined significantly from study entry levels.
Conclusions: The majority (51%) of the participants discontinued 6-months of nightly hypnotic use. Higher depression scores (BDI II) were predictive of difficulty discontinuing chronic hypnotic use.
Financial Support: NIDA, grant#: R01DA038177 awarded to Dr. Roehrs.

ORAL SESSION: UNVEILING THE FRAMEWORK: STRUCTURAL-LEVEL FACTORS AND THEIR IMPACT ON SUBSTANCE USE

Cumulative Racism and Substance use: Results from the 2023 Racism and Public Health Study

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Drug Category: Other, Substance Use Disorders
Topic: Racial/Ethnic Differences
Abstract Detail: Other
Abstract Category: Original Research
Aim: Racial discrimination has deleterious effects on mental and physical health, but its contribution to substance use outcomes is unknown. We explore associations between exposure to racism across the life course, substance use disorder (SUD), and reporting substance use as a coping mechanism for discrimination among US adults.
Methods: Data from a web-based cross-sectional survey of N=5,059 adults were used. Exposure to racism in childhood, adolescence, adulthood, and within the past year was measured on a Likert Scale, dichotomized within each period, and summed to produce a cumulative life course racism score (range 0-4). Lifetime SUD

diagnosis (yes/no), reported coping with substances ('Often/usually/always' vs. 'Never/rarely/sometimes') and sociodemographic and structural were measured. Multiple logistic regression models were used to i) explore associations between cumulative racism exposure and odds of SUD diagnosis overall and stratified by race, and ii) identify correlates of coping with substances among those with exposure to racism.
Results: After adjusting for age, gender, homelessness, employment, and education, greater exposure to life course racism was associated with higher odds of SUD among Black (OR: 1.4; p=0.009) and Hispanic (OR:1.4; p=0.029) participants only. Among participants of all races experiencing racism in ≥1 life stage (N=2,387), those who were younger, male, experiencing food, housing, or financial insecurity, had dependents, and reported greater cumulative exposure to racism ($p<0.001$ for all) were more likely to report coping with substances in a fully adjusted model.
Conclusions: Findings suggest that cumulative exposure to racism is independently associated with lifetime SUD diagnosis among Black and Hispanic populations, who are currently experiences the steepest increases in overdose mortality. We further identify subgroups who report coping with discrimination by using substances, which may be useful for informing and targeting interventions to mitigate the possible impacts of discrimination on incidence and progression of SUD.
Financial Support: None

Drug Use-Related Discrimination in Healthcare Settings and Subsequent Emergency Department Utilization in a Prospective Cohort Study of People With a History of Injection Drug Use

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Drug Category: Other, Injection drug use
Topic: Other, Stigma and discrimination
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research
Aim: People with a history of injection drug use face discrimination in healthcare settings that may impede their use of routine care, leading to greater reliance on the emergency department (ED) for addressing health concerns. This study aims to document the association between drug use-related discrimination in healthcare settings and subsequent ED utilization among a cohort of people with a history of injection drug use.
Methods: This study used longitudinal data collected between January 2014 and March 2020 from participants of the ALIVE (AIDS Linked to the IntraVenous Experience) study, a community-based observational cohort study of people with a history of injection drug use in Baltimore, Maryland. 1,342 participants contributed data from 7,289 semi-annual study visits. Logistic regressions with generalized estimating equations were used to estimate associations between drug use-related discrimination in healthcare settings and subsequent ED utilization. Adjusted models included past six-month ED and drug use as well as self-rated need of healthcare, having a consistent source of primary care, insurance status, and age. Associations were estimated for the total sample and strata of race, sex, and HIV status.
Results: Participants were predominately Black (82%), mostly male (66%), and 33% were living with HIV. Those who reported drug use-related discrimination in healthcare settings (reported at 6% of study visits) were significantly more likely to report ED use at the next study visit (OR=1.40, 95% CI: 1.15-1.72). These associations persisted after adjustment for covariates for the total sample (aOR=1.28, 95% CI: 1.04-1.59) and across strata of race, sex, and HIV status, though not all associations retained statistical significance.
Conclusions: Drug use-related discrimination in healthcare settings was associated with greater subsequent ED utilization in this sample. Further exploration of the mechanisms driving this relationship may help improve care and optimize healthcare engagement for people with a history of injection drug use.
Financial Support: This study was supported by the National Institute on Drug Abuse (NIDA) (U01DA036297). The study was also supported by the Johns Hopkins University Center for AIDS Research (CFAR), an NIH funded program (10P30AI094189), which is supported by the following NIH Institutes: NIAID, NCI, NICHD, NHLBI, NIDA, NIA, NIGMS, NIDDK, NIMHD. ELE is supported by the National Institutes of Health, National Institute on Drug Abuse (NIDA) (T32DA031099). EUP was supported by NIDA (F31DA054849) and NIAID (T32AI102623).

Instability of Insurance Coverage in Patients on Buprenorphine and Naltrexone for Opioid Use Disorder: Evidence From Three US Health Systems

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Drug Category: Opiates/Opioids
Topic: Health Services
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research

Aim: We examined health plan disenrollment and associated factors in patients on medication for opioid use disorder (MOUD).
Methods: In this retrospective cohort study of patients age ≥16 on buprenorphine or naltrexone between 2012-2021 from 3 health systems, we calculated the frequency of health plan disenrollment within 12 and 24 months after the first observed MOUD (index) treatment episode. We fit Poisson models to identify patient characteristics associated with disenrollment rates, defined as the number of disenrollments per person-years of follow-up. Characteristics examined included patient demographics, insurance type, medications (e.g., opioid analgesics and benzodiazepines), substance use disorders, mental health disorders, and other comorbidities.
Results: The cohort included 22,938 MOUD patients with a mean (median) age of 38.7 (36), of whom 62% were men, 5% Black, 78% White, 17% other or missing race, and 19% Hispanic of any race. Further, 84% had commercial insurance, 12% had Medicare, 6% had Medicaid, and 6% had other insurance (not mutually exclusive). The mean (median) length of treatment episodes was 506 (130) days. Within 12 and 24 months of the index treatment episode, 6,161 (26.9%) and 9,525 (41.5%) patients, respectively, had ≥1 disenrollments on or off treatment. Additionally, 1,898 (8.3%) and 2,698 (11.5%) patients had ≥1 disenrollments while on treatment within 12 and 24-months from the index episode, respectively. In an adjusted model, the estimated risk of disenrollment was higher for ages 16-25 (IRR=1.80, 95% CI 1.63-1.99) and 26-45 (IRR=1.40, 95% CI 1.40-1.66) compared to ages 46-64. Further, the estimated risk was lower for patients with Medicare compared to those without Medicare (IRR=0.73, 95% CI, 0.62-0.84). Results were similar for disenrollment while on treatment.
Conclusions: In this cohort of patients on MOUD, more than 40% disenrolled from health plans within two years of treatment. Findings suggest that disenrollment may contribute to poor treatment retention, especially in younger patients.
Financial Support: This study is supported by a grant from the National Drug Abuse Treatment Clinical Trials Network (CTN-0141) of the National Institute on Drug Abuse (3UG1DA040314-08S4).

An Intersectional and Spatial Approach to Assessing the Relationship Between Structural Racism and Opioid-Involved Overdose Deaths in Chicago, Illinois

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Drug Category: Opiates/Opioids
Topic: Disparities, Structural Racism and Overdose
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research

Aim: Over the last decade, the opioid overdose crisis has been marked by a dramatic increase in opioid-involved overdose deaths among racially minoritized populations. There is increasing interest in structural drivers of overdose; this research investigates the relationship between structural racism and overdose.
Methods: We performed an intersectional and ecological cross-sectional study of 797 census tracts in Chicago, Illinois, from 2017 to 2019. We utilized two indicators to operationalize structural racism: historical

redlining and contemporary racialized economic segregation. For each tract, the redlining and segregation scores were dichotomized, signifying the level of social and economic disadvantage or advantage by tract. Cross-classification of the redlining and segregation variables generated four intersectional groups. We aggregated all fatal opioid-involved overdoses to the tract level and derived a tract-level count for opioid-involved overdose deaths. We conducted a quasi-Poisson regression to determine associations between our intersectional groups and tract-level opioid-involved overdose deaths. To reduce residual spatial autocorrelation, we ran a spatial regression using eigenvector spatial filtering; we also controlled for population density in our model.
Results: Sustained disadvantaged tracts—tracts that were historically redlined and experienced high contemporary racialized economic segregation— had over four times higher rates of fatal opioid overdoses (IRR= 4.02; 95% CI: (2.68, 6.30; p>0.001) compared to sustained advantaged tracts—tracts that were not historically redlined and experienced low contemporary segregation.
Conclusions: Our study introduces an intersectional approach to investigating the underexplored research area of structural racism and opioid-involved overdose. These findings provide preliminary evidence that structural racism could be a root cause of opioid-involved overdose deaths. Future research is needed to identify mechanisms linking structural racism to overdose deaths. Moreover, further intersectionality research studies may identify structural determinants of substance use-related outcomes, including overdose, which policies and programs can ultimately target.
Financial Support: This study is funded by the T32 Drug Dependency Epidemiology Training Program (T32DA007292) at the Johns Hopkins Bloomberg School of Public Health

ORAL SESSION: I THOUGHT OF IT FIRST! - INNOVATIONS IN APPLICATIONS, MODELS, AND ANALYSIS

Novel Intervention to Improve Food Insecurity among Individuals with Opioid Use Disorder

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Drug Category: Opiates/Opioids
Topic: Comorbidities
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research
Aim: The adverse consequences of illicit opioid use (e.g., overdose, infectious disease) have been the focus of intensive research efforts. However, other serious health problems among individuals with OUD have received far less attention. Food insecurity (FI) is 4-7 times greater among individuals with OUD than the general US population and associated with increased drug use, sexual and drug risk behaviors and a two-fold risk of premature death. Aim to evaluate the feasibility, acceptability and initial efficacy of a meal delivery intervention for reducing FI among adults with OUD.
Methods: Methods: Participants (n=50) who were enrolled in MOUD treatment and met criteria for FI (GREATER THAN 3 on the US Household Food Security Survey (FSS)) were randomized to one of two 12-week conditions. Nutritional Education (NE; n=25) participants received brief NE, a list of FI-related community resources, and assistance contacting resources of interest. NE+Meal Delivery (NE+MD; n=25) participants received NE plus premade, refrigerated meals delivered weekly by a commercial service. Both groups completed monthly assessments of FI, dietary intake, nutrition knowledge and psychosocial functioning.
Results: Results: Participants were 39.2+7.3 years old, 58% female and 82% white. Participants' mean baseline FSS score was 8.2+3.1. Following randomization, retention was similar between the two groups (88% and 84% in NE+MD and NE conditions, respectively). NE+MD participants demonstrated significantly greater decreases from intake in FSS score vs. controls, with mean FSS scores lower in NE+MD vs. control participants at all three post-intake timepoints (p's<.05). Among NE+MD participants, a total of 2,976 meals were successfully delivered and meal enjoyment and convenience were rated at 81 and 93, respectively (range:0-100).

Conclusions: Conclusion: Preliminary results suggest the initial feasibility, acceptability and efficacy of this intervention for improving FI among individuals with OUD. Complete primary and secondary outcomes will be available for the June 2023 meeting.
Financial Support: Supported by departmental funds (Sigmon) and a NIDA training grant (T32DA007242)

Microdosing Partial Agonists Inactivates Kappa Opioid Receptors - An Alternative Strategy for Human Trials

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Drug Category: Opiates/Opioids
Topic: Treatment
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research
Aim: Preclinical studies have highlighted the crucial role of the Kappa opioid receptor (KOR)/dynorphin system in the development of stress-related anxiety, dysphoria, cognitive disruption, and addictive behaviors. The therapeutic promise of KOR antagonists that can inhibit these endogenous dynorphin effects is increasingly evident. This study utilized daily dosing with either nalfurafine—a G-biased KOR agonist—or nalmefene—a mu-opioid antagonist and partial KOR agonist to inactivate KOR through the established JNK-ROS mechanism.
Methods: 7-day treatment of adult C57BL/6 mice with various doses of norBNI, nalmefene, nalfurafine, or vehicle. KOR-mediated analgesia, aversion, fentanyl withdrawal, prolactin release, diuresis, and antipruritic effects were assessed (n = 6-16). KOR activation of JNK was measured using a novel ROS sensor (oROS-Gr) in the VTA of KOR-Cre mice (n = 4-12).
Results: Results demonstrate that repeated, low doses of nalmefene or nalfurafine effectively blocked KOR-induced analgesia ($p > 0.01$) and aversion ($p > 0.05$). No impact on diuresis or itch inhibition was observed. Acute doses of nalmefene or nalfurafine stimulated oROS-Gr, indicating KOR activation of JNK and downstream stimulation of ROS production. This response was blocked by naloxone (opioid antagonist), JNK-IN-8 (JNK inhibitor), or MJ33 (PRDX6 inhibitor). Interestingly, the study uncovers estrus cycle-dependent variations in KOR activation, highlighting the importance of hormonal states in modulating drug effects. Recovery of KOR responses post-treatment required over two weeks.
Conclusions: These findings suggest that chronic low-dose treatment with nalfurafine or nalmefene could offer a safer, more targeted approach to KOR inactivation, with fewer side effects compared to competitive KOR antagonists. The observed tissue-specific effects, with no interference in diuretic or antipruritic responses, indicate tissue-specific selectivity. The lower doses required for KOR inactivation may minimize off-target adverse effects, making them attractive candidates for prolonged use and highlighting their potential to promote stress resilience with therapeutic selectivity.
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Using Rodent Models to Uncover Behavioral and Biological Predictors of Cannabis Use

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Drug Category: Cannabis/Cannabinoids
Topic: Neurobiology/Neuroscience
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research
Aim: Approximately 9% of first-time cannabis users will become dependent on cannabis, yet there are no FDA-approved pharmacotherapies for managing cannabis use disorder (CUD). This is in part due to flawed diagnostic nosology resulting in a lack of understanding of the mechanisms that give rise to CUD, as well as

a conspicuous lack of translationally relevant animal models of cannabis use. To address these gaps, we have developed and validated a novel model of cannabis self-administration that delivers vaporized cannabis extracts in a response-contingent manner via the pulmonary route of administration that is most common among human users. Our data indicate that rats exhibit stable rates of responding for cannabis vapor that produce dose-dependent elevations in plasma Δ9-tetrahydocannabinol (THC) concentrations and metabolic alterations that are consistent with observations in human cannabis users. We used this model in the present studies to identify behavioral and biological factors that predict high vs. low rates cannabis-seeking behavior and determine alterations in the endocannabinoid (ECB) system following vapor self-administration.

Methods: We conducted an extensive battery of behavioral assays in female and male Long Evans rats (N=48) prior to initiation of cannabis self-administration training and characterized endophenotypes using endpoints that correspond to the behavioral dimensions of the NIMH Research Domain Criteria (RDoC). We then used a series of linear regression analyses to determine whether behavioral and physiological parameters in the five RDoC dimensions (positive and negative valence systems, cognition, social processes, and arousal/regulatory systems) significantly predicted the number of cannabis vapor deliveries earned during a progressive ratio test after four weeks of cannabis self-administration.

Results: The Arousal/Regulatory Systems model was significant, accounting for 43.3% of the variance in cannabis self-administration. Specifically, higher concentrations of basal corticosterone (CORT) predicted higher rates of cannabis vapor self-administration, while lower concentrations of stress-induced CORT predicted lower rates of self-administration. The Cognition model was also significant, accounting for 17.9% of the variance in cannabis self-administration. Specifically, better visual cue discrimination and poorer set shifting performance each predicted higher rates of cannabis vapor self-administration. Additionally, the Positive Valence model was significant, accounting for 21.1% of the variance in cannabis self-administration, with greater motivation for sucrose reinforcement predicting higher rates of cannabis vapor self-administration. Finally, the Social Processes and Negative Valence models were not statistically significant predictors of cannabis self-administration.

Conclusions: Overall, our data indicate that basal/stress-induced CORT, high motivation for sucrose reinforcement, and greater reliance on visual cue-based strategies were all significant predictors of motivation to self-administer cannabis vapor in adulthood. These data suggest that neuroendocrine alterations and enhanced cue sensitivity may precede the onset of problematic cannabis use, which could be leveraged to identify individuals with increased susceptibility for developing CUD. Ongoing studies are currently measuring AM and PM concentrations of circulating eCBs (AEA and 2-AG) as another potential predictor of cannabis self-administration and exploring whether chronic cannabis vapor self-administration alters eCB content relative to vehicle vapor self-administration.

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A Simplified Model of Behavioral Economic Demand That Produces Estimates Consistent With the Common Exponentiated Model

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Drug Category: Alcohol
Topic: Behavioral Economics
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research

Aim: Behavioral economic demand is a popular method for assessing the reinforcing value of substances, but existing models present challenges with modeling of zeros, correlated parameters, and additional span parameters. The purpose of this study was to analyze alcohol and cigarette demand data and compare a simplified model of demand based on Samuelson's discounted utility function (1937) and the exponentiated model of demand (Koffarnus et al., 2015).

Methods: Hypothetical alcohol and cigarette purchase data from baseline assessments from an ongoing alcohol treatment study involving community and inpatient alcohol detoxification populations were used to compare the simplified and exponentiated models of demand. Goodness-of-fits, correlations between parameter estimates from different models, and statistical conclusions were used to determine similarities between the models of demand.

Results: Median and overall goodness-of-fit values (i.e., R2) were within .02 between models, indicating both models provided similar descriptions of the data. Parameter estimates between the two (α and Q0) were also highly correlated across models (rs< .99). Lastly, statistical conclusions between the two models when using a significance criterion of α = .05 resulted in the same decisions regarding differences in parameter estimates based on group.
Conclusions: The simplified model of demand based on Samuelson's discounted utility function performed nearly identically to the exponentiated model of demand, the current gold standard of non-linear modeling of demand data. However, this simplified model removes the need for a span parameter, as well as allows for analytic solutions to other demand metrics. This simplified model can decrease the variability of analyses while retaining the benefits of previously established models of demand.
Financial Support: R01 AA026605

ORAL SESSION: FROM HORSE TO HUMAN: UNDERSTANDING XYLAZINE AND OPIOID EFFECTS

Suppression of Fentanyl Consumption by Xylazine Tolerates with Extended Access and Induces Hyperglycemia in Female Rats

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Drug Category: Opiates/Opioids
Topic: Substance Use Disorder
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research
Aim: The aim of this study is to evaluate fentanyl consumption patterns under extended access conditions when xylazine is included in the fentanyl infusion and evaluate the impact of xylazine on blood glucose levels.
Methods: 10 female Long Evans rats underwent jugular vein catheter surgery followed by 7 sessions of 1 h fentanyl SA (3.2 μg/kg/infusion). Rats were then assigned to either 6 h fentanyl (same dose) or fentanyl+xylazine (same fentanyl dose, 0.15 mg/kg/infusion xylazine) SA based on non-significant baseline differences in fentanyl consumption during acquisition. Rats then underwent an additional 10 sessions of 6 h access. Blood glucose testing was evaluated at baseline (pre-experimentation), after day 7 acquisition, and finally after day 10 of extended access via tail vein bleed and glucometer.
Results: Fentanyl consumption was suppressed by xylazine during the first 6 sessions of extended access, and then increased between sessions 7-10. There was a main effect of group ($F_{1,9} = 13.08$, $p<0.05$) indicating that the fentanyl+xylazine group self-administered significantly less fentanyl than the fentanyl alone control group, but there was no main effect of session or session x group interaction. Glucose testing revealed significantly lower blood glucose levels following fentanyl SA acquisition compared to baseline, which continued after extended access sessions ($F_{3,28} = 25.05$, $p<0.05$). Rats in the fentanyl+xylazine group demonstrated significantly higher blood glucose levels compared to baseline and compared to the fentanyl alone group after extended access.
Conclusions: Together, these results show that the suppression of fentanyl consumption by xylazine may tolerate with extended access, and that while SA of fentanyl alone induces hypoglycemia, SA of the fentanyl and xylazine combination induces hyperglycemia which has important translational implications for glucose toxicity, diabetes, and insulin resistance.
Financial Support: National Institute on Drug Abuse grant R01 DA058933 (to CDG and TDH), R01DA046526, R33 DA049130, R21 DA055879 (to CDG).

Fentanyl and Xylazine Concentrations in Urine Predict Detection Times in Clinical Trial Participants

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Drug Category: Polydrug (i.e. concurrent use two or more drugs)
Topic: Other, Pharmacology
Abstract Detail: Clinical - Experimental
Abstract Category: Original Research

Aim: Reports suggest persons who use illicit fentanyl test positive for fentanyl and norfentanyl in urine longer than established toxicology detection windows, and the excretion profile of xylazine in clinical populations is unknown. This study examined the detection time for fentanyl, norfentanyl, and xylazine.
Methods: Participants with fentanyl exposure presenting for a residential study provided up to 4 urine samples daily for 5 days. Urine concentrations of fentanyl, norfentanyl, and xylazine were determined quantitatively via a selected reaction monitoring-based liquid chromatography-mass spectrometry assay (lower limit of quantitation [LLOQ] 5 ng/mL for all analytes). Detection times were normalized to the participant's most recent self-reported fentanyl use. Using a non-compartmental pharmacokinetic modeling approach applied to the spot urine samples, we predicted when each participant's urine analyte concentrations were expected to fall below 5 ng/mL.
Results: Eleven participants provided at least three urine samples between May 2022 and January 2023. Participants were majority male (82%), of black (55%) or white (45%) race, with an average age of 42 years. Most reported intranasal (82%) versus intravenous (18%) fentanyl use. Ten participants (91%) had at least one urine sample with quantifiable xylazine. Predictions were included if analyte line R2 GREATER THAN 0.5 and/or the prediction line confirmed when the analyte fell below LLOQ. Fentanyl's average predicted detection time was 74.3 hours (SD=40.2 hours, N=7, 2 confirmed). Norfentanyl's average predicted detection time was 136.0 hours (SD= 64.3 hours, N=4). Xylazine's average predicted detection time was 31.2 hours (SD=16.7 hours, N=7, 3 confirmed).
Conclusions: Since our LLOQ is higher than many qualitative urine drug tests, we predict persons with illicit fentanyl exposure will test positive for an extended time (GREATER THAN 3 days). This is also the first study to characterize urinary detection time of xylazine, which may be helpful in developing urine toxicology tests.
Financial Support: NIGMS (T32GM66691) and NIDA (UH3DA048734)

A Novel Approach to Treat Xylazine and Opioid Intoxication

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Drug Category: Polydrug (i.e. concurrent use two or more drugs)
Topic: Treatment
Abstract Detail: Preclinical - In Vivo
Abstract Category: Original Research

Aim: The aim of this abstract was to evaluate the efficacy of CS-1103 in reversing toxicity of xylazine and fentanyl in rat.
Methods: We used a rat model in this study. Fentanyl (100 μg/kg) and xylazine (3 mg/kg) were given to rats followed by administration of CS-1103 or saline control. Respiration and sedation were recorded before and after treatment. Urine samples were collected and the amount of fentanyl and xylazine in urine was quantified using a HPLC-MS method. Both male and female animals are used in the study. Descriptive data are reported as mean (standard error of the mean); change rates are reported with 95% confidence intervals. A two-tailed paired t-test was used to calculate p-values; $p<0.05$ is considered statistically significant.
Results: CS-1103 restored respiration in 2-3 min, reversed sedation caused by xylazine in 10-20 min ($p<0.0001$), and accelerated clearance of fentanyl and xylazine into urine 73-fold and 7-fold ($p<0.0001$), respectively, in 2 hr, vs saline control. In contrast, naloxone was less effective in restoring respiration, and showed no improvement in sedation reversal or intoxicant clearance vs saline control.
Conclusions: CS-1103 is effective in reversing fentanyl and xylazine toxicity.

Financial Support: NIH/NIDA: 1R43 DA052957-01, 1R43 DA056272-01, 2R44 DA05295702, and 3U01 DA053054-02S1

Self-Reported Knowledge, Preference, and Perceived Effects of Xylazine among Adults in Substance Use Disorder Treatment

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Drug Category: Opiates/Opioids
Topic: Epidemiology, Xylazine
Abstract Detail: Clinical - Epidemiology
Abstract Category: Original Research

Aim: The study investigates the presence and impact of xylazine, a veterinary tranquilizer, in non-medical opioids among individuals seeking substance use disorder treatment in the USA.
Methods: Individuals (n=2,872) in 78 substances use treatment programs in the USA who reported non-medical opioid use within 30 days before treatment were surveyed, from January to October of 2023, about their awareness, of xylazine, preference of xylazine, side-effects of xylazine, and changes in withdrawal. Data were collected from January to October 2023 byTrac9, a commercial treatment outcomes provider and analyzed with chi squared and logistic regression.
Results: Less than half (45%) of respondents were aware of xylazine, with higher awareness among those primarily using opioids. Over 95% of those aware did not want xylazine in their opioids, and about 85% did not prefer opioids containing xylazine. Overall, 68.4% reported experiencing, at least one, xylazine-related side effect and 40.5% reported altered withdrawal symptoms. Results of logistic regression demonstrate that the more likely that an individual believed that their opioids had been adulterated were also more likely to report experiencing side-effects of xylazine us (i.e., skin lesions, increased sedation, loss of consciousness, and difficulty in reversing overdoses with naloxone) as well as increased headaches and a sensation of burning particularly when administered naloxone.
Conclusions: The study underscores the widespread lack of xylazine awareness among opioid users in treatment, coupled with concerning side effects and altered withdrawal symptoms. However, as the study sample was limited to treatment program attendees, generalizability might be restricted. The findings stress the critical need for harm reduction strategies to increase public awareness about xylazine, aiming to mitigate its exposure and associated risks. This study sheds light on the urgent necessity for interventions to address the lack of knowledge surrounding xylazine and its adverse effects among individuals using opioids.
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