Tuesday, June 20, 2023
Late-Breaking Oral Session 1
Governor's Square 15

Bacterial and Fungal Infections: An Underrecognized Cause of Death Among People With Drug Use Diagnoses

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Select Drug Category Other, Several drug categories and drug use-associated infections
Topic Epidemiology
Abstract Detail Clinical - Epidemiology
Abstract Category Original Research
Aim: As the overdose crisis has worsened, drug use-associated bacterial and fungal infections have also increased. While overdose mortality is commonly reported, the extent to which these infections contribute to mortality is not described. We aimed to estimate the incidence of mortality from bacterial and fungal infection-related and overdose among people with drug-use related visits.
Methods: A cohort design was used to study publicly and privately insured adults in North Carolina with drug use diagnoses during January 1, 2007, through December 31, 2018. We linked these claims to NC death certificates. We assessed bacterial and fungal infection-associated mortality two related but distinct methods: Definition A included those with diagnostic codes for invasive infection-associated hospitalizations (e.g., infective endocarditis, septic arthritis, osteomyelitis) in the 30 days prior to their death. Definition B used codes for invasive infection or sepsis on the death certificates. We estimated the 1-year incidence of mortality using Aalen-Johansen cumulative incidence functions.
Results: Of the 131,522 people with drug use diagnoses included, the median age was 45 years (IQR: 31-57), 65% had an opioid use disorder diagnosis, 31% had a stimulant use disorder diagnosis, and 13% had a sedative or hypnotic use disorder diagnosis. Within the first year of follow up, overdose mortality incidence was 36 per 10,000 people (95%CI: 33-40). Bacterial and fungal infection-associated mortality varied by definition (A vs. B) and ranged from 16 per 10,000 people (95%CI=14-18) for Definition A to 43 per 10,000 people (95% CI=39-47) for Definition B. Bacterial and fungal infection-associated mortality was higher as age increased. In contrast, overdose mortality was higher among younger adults.
Conclusions: Both bacterial and fungal infections and overdose were contributors to mortality among people with drug use diagnoses. Although our estimates varied by definition, incidence of fatal infection may approach overdose among sub-populations.
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First in the World Trial of low Intensity Focused Ultrasound for Substance Use Disorder

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Select Drug Category Polydrug (i.e. concurrent use two or more drugs)
Topic Technology (e.g., mHealth)

Abstract Detail Clinical - Experimental
Abstract Category Original Research
Aim: We initiated an FDA clinical trial to assess the safety, tolerability, and feasibility of Low Intensity Focused Ultrasound (LIFU) applied to the nucleus accumbens (NAc) in participants with opioid and co-occurring substance use disorders (SUD). Secondary aims include evaluating the impact of LIFU on substance craving.
Methods: Six participants with SUDs received sham LIFU followed by active LIFU sonications targeting the NAc either sequentially (left then right NAc; Participants #1 and #2) or simultaneously (bilaterally; Participants #3-6). Safety outcomes were assessed during the procedure and throughout the 90-day follow-up. Secondary outcomes included the acute (during, and immediately following LIFU sonications) and long-term assessment (up to 90-day) of cue-induced craving using a visual analog scale (0=no craving to 10=most craving ever).
Results: LIFU applied to the NAc was safe and well-tolerated in all participants. Sham sonication resulted in no appreciable craving changes ($p>.05$). Relative to baseline craving and sham sonication, enhanced NAc LIFU acutely attenuated self-reported craving for all substances (mean reduction: >50%). Reduction in craving for the participants' most craved drugs was sustained during follow-up ($p=.004$; mean±SD: baseline 5.02±2.7; follow up 0.17±0.40). Moreover, participants remained abstinent from all illicit substances, verified by urine toxicology.
Conclusions: This is the first investigation of LIFU targeting the NAc in individuals with SUD. The procedure was safe and well-tolerated, LIFU acutely reduced cue-induced substance craving during sonication. Unexpectedly, this dramatic reduction in craving was sustained through to long-term follow up. Prior to LIFU these participants struggled with persistent craving and were unable to maintain abstinence. While promising, NAc LIFU requires further investigation in a randomized, controlled trial with a larger cohort of participants to further establish safety, determination of optimal treatment parameters, prolonged impact on craving and other critical outcomes.
Financial Support: Internal funding from Rockefeller Neuroscience Institute West Virginia University

Known Fentanyl Use and Potential Reasons for Non-Use of Fentanyl Test Strips Among People who Use Drugs

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Select Drug Category Polydrug (i.e. concurrent use two or more drugs)
Topic Harm Reduction
Abstract Detail Other
Abstract Category Original Research
Aim: New York City faced a record number of fatal overdoses in 2021, largely due to fentanyl, which was present in more than 80% of overdose deaths. Fentanyl test strips (FTS) and other methods can be used to determine the presence of fentanyl before people use potentially deadly drug batches. We examine why some at greatest risk may choose not to test.
Methods: Our team is currently conducting a pragmatic trial designed to increase COVID vaccination among people who inject drugs. We have partnered with a community-based organization providing services to people in NY neighborhoods with high overdose rates, including East Harlem and the Bronx. To better understand participants' fentanyl use, we included questions in a substance use screening. We conducted a 6-person focus group discussion with our community advisory board about FTS use.
Results: Of 138 trial participants, 49 identified as Hispanic or Latino, and 36 identified as non-Hispanic Black. In response to the question "On how many days in the past 30 did you knowingly use fentanyl?", 61% reported at least one, with more than 20% reporting daily use. Of six focus group participants who reported current or former opioid drug use, all described not using FTS because they did not want to waste time or "product", and they assumed that fentanyl would be in any heroin purchased. They also reported they could identify fentanyl by color and texture, and consumed more carefully if the presence of fentanyl was suspected. While they understood the danger of fentanyl overdose, all described themselves as unlikely to use FTS due to the barriers noted above.

Conclusions: Our data underscore the widespread consumption of drugs known to contain fentanyl, and indicate that people with access to FTS may choose not to use them. Efforts are needed to increase use of drug checking for overdose prevention.
Financial Support: R01DA054990

Respiratory Depressant Effects of Fentanyl in Combination With Synthetic Cannabinoid Receptor Agonists: A Potential Mechanism for "Narcan-Resistant" Overdose

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Select Drug Category Polydrug (i.e. concurrent use two or more drugs)
Topic Drug Interactions
Abstract Detail Preclinical - In Vivo
Abstract Category Original Research
Aim: Reports of "Narcan-resistant" opioid overdose have proliferated in the media. One mechanism for this treatment resistance could be contamination of the opioid with a non-opioid drug which also suppresses respiration. The most commonly detected adulterants in street opioids are synthetic cannabinoid receptor agonists (SCRAs), which are not standard analytes in emergency toxicology screens. Limited evidence from humans and laboratory animals suggests that SCRAs depress respiration. We hypothesized that co-administration of fentanyl (FEN) with a SCRA would suppress respiration in an additive or synergistic manner, and that these effects would be resistant to reversal with naloxone.
Methods: Whole body plethysmography characterized respiratory depressant effects of the μ-opioid FEN and the SCRAs JWH-018 and 5F-ADB-PINACA, alone and in combination, in adult male NIH Swiss mice. The μ-antagonist naloxone, the CB1 antagonist rimonabant, or both antagonists together were also administered with FEN and the SCRAs.
Results: FEN and both SCRAs rapidly elicited respiratory depressant effects at similar doses, and the magnitude of these effects was similar across drugs. Naloxone attenuated respiratory depressant effects of FEN, but not those of the SCRAs, while rimonabant attenuated the effects of the SCRAs, but not those of FEN. Combining small doses of FEN and the SCRAs produced additive respiratory depressant effects. Attempts to "rescue" mice treated with the FEN + SCRA combination using a very large dose of naloxone only partially reversed respiratory depression. Similarly, "rescuing" mice with a large dose of rimonabant only partially reversed respiratory depression. Co-administration of the large doses of both antagonists also failed to fully reverse the respiratory depressant effects of FEN + SCRA.
Conclusions: Co-administration of opioids with SCRAs exacerbates respiratory depression and decreases the effectiveness of naloxone as an overdose reversal agent. Emergency toxicology screens should test for SCRAs during opioid overdose.
Financial Support: None

Preclinical Evidence Supporting the Repurposing of Suvorexant (Belsomra™) to Manage Sleep Disturbances During Initial Cocaine Abstinence

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Select Drug Category Stimulants
Topic Treatment
Abstract Detail Preclinical - In Vivo
Abstract Category Original Research
Aim: A recent study reported that the sleep medication suvorexant (Belsomra™), a dual orexin receptor antagonist, improves sleep and withdrawal outcomes in persons with opioid use disorder during a buprenorphine/naloxone taper. The aim of this study was to test if suvorexant might have similar efficacy in normalizing sleep disturbances during initial cocaine abstinence in rats.
Methods: In one set of studies, we induced a conditioned place preference (CPP) to non-contingent cocaine injections (10mg/kg) in male Long Evans rats (n=9). CPP was extinguished across 5 daily extinction sessions. In a second set of experiments, female Sprague Dawley rats (n=9) were trained to self-administer

cocaine on an intermittent access schedule for 14d before undergoing extinction training. In both groups, rats received suvorexant (0, 30 mg/kg, p.o) immediately prior to the onset of the inactive period during extinction. Sleep was monitored during cocaine exposure and the suvorexant treatment period using electroencephalogram (EEG) and electromyogram (EMG) recordings. All data were analyzed using mixed-model ANOVA.
Results: Cocaine abstinence was associated with increased time spent in active wake, reduced time spent in rapid eye movement (REM) and non-REM sleep, and increased sleep fragmentation (all p's<0.05, vs. baseline). Suvorexant normalized sleep outcomes (active wake, REM, non-REM sleep: p's<0.01; fragmentation: p<0.05) and facilitated extinction of both CPP and lever responding (p's<0.05).
Conclusions: Suvorexant normalizes sleep disturbances associated with initial cocaine abstinence and facilitates the extinction of cocaine seeking behaviors. These data support the potential repurposing of suvorexant for the management of cocaine use disorder.
Financial Support: NIDA R00 (045765) and Busch Biomedical Grant to MHJ.

Association Between Prescribed Stimulant Medications and Overdose Among Individuals Receiving Opioid Agonist Therapy: A Retrospective Cohort Study From British Columbia, Canada

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Select Drug Category Stimulants
Topic Epidemiology
Abstract Detail Clinical - Epidemiology
Abstract Category Original Research
Aim: Healthcare practitioners may hesitate to prescribe stimulants to individuals on opioid agonist therapy (OAT) due to perceived risks. We examined the association between co-prescribed stimulant medications and overdose among individuals receiving OAT.
Methods: We used the British Columbia Provincial Overdose Cohort, a linked administrative database, to create a retrospective cohort of male and female individuals dispensed oral OAT (methadone, buprenorphine/naloxone, or slow-release oral morphine) for opioid use disorder from January 2015 through February 2020. We fit a multivariable extended Cox model to examine the association between stimulant prescription and fatal or non-fatal overdose, adjusting for potential confounders. As a secondary analysis, we evaluated type of OAT (full agonists involving methadone or slow release oral morphine versus partial agonist involving buprenorphine/naloxone alone) as a potential effect modifier.
Results: In total, 9395 eligible individuals contributed 18,273 person-years of follow-up. Median age was 36 years (interquartile range 29-47) and 2989 (31.8%) were female. A stimulant medication was dispensed 532 (2.9%) person-years of follow-up. There were 1746 overdose events; 37 (2.1%) were fatal. Overall, there was no increased risk of overdose among individuals co-prescribed a stimulant medication (adjusted hazard ratio [aHR] 1.13, 95% Confidence Interval [CI] 0.86-1.49, p=0.39). When analyzed by type of OAT medication as an effect modifier, stimulant medication dispensation alongside buprenorphine/naloxone was associated with a reduced risk of overdose (aHR 0.47, 95%CI 0.23-0.97, p=0.037) while dispensation alongside a full agonist was associated with an increased risk of overdose (aHR 1.51, 95%CI 1.09-2.07, p=0.012).
Conclusions: We found that co-prescribed stimulant medication with OAT is not associated with an increased risk of overdose. However, our secondary analysis suggests that co-prescribed stimulants alongside full agonist OAT (methadone or slow-release oral morphine) is associated with an increase in overdose, while buprenorphine/naloxone is associated with a decrease. Additional study is indicated to further clarify this relationship.
Financial Support: Samantha Young is supported by the Canadian Institutes of Health Research Vanier Canada Graduate Scholarships and the International Collaborative Addiction Medicine Research Fellowship (NIDA grant R25-DA037756). Seonaid Nolan is supported by the University of British Columbia's Steven Diamond Professorship in Addiction Care Innovation.

PET Imaging of Kappa Opioid Receptors in Socially Housed Female and Male Monkeys: Effects of Chronic Cocaine Self-Administration

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Select Drug Category Stimulants
Topic Imaging
Abstract Detail Preclinical - In Vivo
Abstract Category Original Research
Aim: There remains no FDA-approved pharmacotherapy for cocaine use disorder (CUD). The kappa opioid receptor (KOR) and its endogenous ligand, dynorphin, are implicated in the neurobiological regulation of stress and CUD. Using positron emission tomography (PET) imaging with the KOR agonist [11C]EKAP in socially housed drug-naïve cynomolgus monkeys, we found significant interactions between sex and social rank in KOR binding potential (BP) that correlated positively with social rank in males and negatively in females (Johnson et al., 2023). The present study extended the investigation of the dynorphin/KOR system using a homologous nonhuman primate model of CUD, involving cocaine self-administration (SA), social behavior, and PET imaging (n=8/sex).
Methods: Utilizing a longitudinal, within-subject design, starting in drug-naïve monkeys, Experiment 1 examined how chronic cocaine SA affected KOR BPs. Following total cocaine intakes of ~100 mg/kg, KOR BP increased (13.0%±1.4%) across all 15 brain regions of interest (ROI) in males; the relationship between baseline BP and cocaine-induced changes correlated positively in 10/15 ROIs. There were no social rank differences observed. In females, the effect of chronic cocaine SA on KOR BP was influenced by social rank, such that cocaine increased KOR BP in dominant females (52%±11%, n=2) and decreased KOR BP in subordinate (-12%±1.6%, n=3) females across all ROI.
Results: The second experiment assessed the neural plasticity of KOR system following protracted time-off from cocaine, by allowing monkeys to respond for 1.0 g food pellets instead of cocaine. Monkeys were rescanned with [11C]EKAP after ~30- and ~100-days off from cocaine. Rate of recovery of KOR BP varied across monkeys and, in some, did not return to baseline after ~100 days off from cocaine.
Conclusions: Future studies will examine how sex and social rank differences in cocaine-induced changes in KOR neurobiology, influence pharmacological interventions, such as KOR antagonists on cocaine-food choice and KOR agonists on punished cocaine SA.
Financial Support: Supported by DA017763-15, DA053776-2

Prescription Amphetamines in People With Opioid Use Disorder and Co-Occurring Psychostimulant Use Disorder Initiating Buprenorphine: An Analysis of Treatment Retention and Overdose Risk

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Select Drug Category Stimulants
Topic Treatment
Abstract Detail Clinical - Epidemiology
Abstract Category Original Research
Aim: To assess the effect of PAs on OUD buprenorphine treatment retention and or substance use disorder (SUD)-related emergency admission or drug-related poisonings in people with and without a co-occurring PSUD.
Methods: We used a retrospective cohort design with a secondary analysis of administrative claims data from Merative™ MarketScan® Commercial and Multi-State Medicaid Databases from January 1, 2006, to December 31, 2016. Individuals included were aged 12-64 and had an OUD diagnosis and were prescribed buprenorphine. Our analysis used multivariable Cox regression to evaluate the relationship between PA receipt (predictor variable) and time to buprenorphine discontinuation (outcome variable). The second part

of our analysis focused on sub-samples of buprenorphine initiators who had either (1) any SUD-related emergency admissions or (2) drug-related poisoning. These outcomes were modeled as a function of PA exposure using conditional logistic regression models as part of a within-person, case-crossover design.
Results: The final sample had 90,269 unique patients with OUD (mean age, 34.2 years [SD=11.3]; 44.2% female; 81.0% non-Hispanic White among Medicaid enrollees) who initiated buprenorphine. Being prescribed a PA was associated with improved buprenorphine retention among individuals both with (aHR, 0.91 [0.86-0.97] and without a concurrent PSUD (aHR, 0.92 [0.90-0.93]). The risk of adverse events associated with PA-treatment days was similar for both individuals with (OR: 0.94 [0.84-1.04] any SUD-related emergency admission; OR: 0.96 [0.75-1.23] drug-related poisoning) and without co-occurring PSUD (OR: 0.82 [0.76-0.88] SUD-related admission; OR: 0.96 [0.84-1.10] drug-related poisoning).
Conclusions: PA use was associated with improved buprenorphine retention in people with OUD, both with and without co-occurring PSUD. The risks of SUD-related emergency admissions and drug-related poisonings associated with PA use did not differ between those with and without co-occurring PSUD.
Financial Support: This project was funded by R21 DA044744 (PI: Richard Grucza/Laura Bierut). Effort for some personnel was supported by grants T32 DA015035 (Kevin Xu, PI: Kathleen Bucholz, Jeremy Goldbach), and by a fellowship from the Saint Louis University Research Institute (Grucza) but these grants did not fund the analyses of the Merative™ MarketScan® Multi-State Medicaid Database data performed by Dr. Xu. In addition, we acknowledge Matt Keller MS, John Sahrmann MS, Dustin Stwalley MA and the Center for Administrative Data Research (CADR) at Washington University for assistance with data acquisition, management, and storage. CADR is supported in part by the Washington University Institute of Clinical and Translational Sciences via grants UL1 TR002345 (from the National Center for Advancing Translational Sciences of the National Institutes of Health).

Prescription Psychostimulant Use in Pregnant People With Opioid Use Disorder: An Analysis of Buprenorphine Retention and Acute Substance Use Disorder-Related Events

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Select Drug Category Stimulants
Topic Prenatal/Perinatal
Abstract Detail Clinical – Epidemiology
Abstract Category Original Research
Aim: In pregnant people with opioid use disorder (OUD) and attention deficit hyperactivity disorder, the risks and benefits of prescription psychostimulant use are poorly understood. We evaluated the association of prescription psychostimulant use in pregnancy with 1) buprenorphine retention and 2) hospitalization or admission for acute substance use disorder (SUD)-related events.
Methods: We conducted a secondary analysis of 1,029 pregnant women with OUD (ages 18-45) in the Merative™ MarketScan® Databases (2006-2016) who were initiating treatment with buprenorphine. OUD and pregnancy status were identified using inpatient and/or outpatient claims for diagnostic (ICD 9/10) or procedure (CPT) codes. The main predictor variable was prescriptions for psychostimulant medication to treat ADHD. The main outcomes were 1) buprenorphine discontinuation and 2) risk of hospitalization or emergency admission for acute SUD-related events and drug-related poisoning. We used multivariable cox regression models to estimate buprenorphine discontinuation. Using a recurrent-event, within-person case-crossover approach, we estimated conditional logistic regression models to evaluate the risk of admission for acute SUD-related events and drug-related poisonings between days with and without psychostimulant exposure.
Results: Prescription psychostimulants were initiated in 14% (n=143) of pregnant women who were starting buprenorphine for the treatment of OUD. In analyses controlling for insurance status, age, and co-occurring psychiatric conditions and SUDs, psychostimulant receipt was associated with decreased likelihood of buprenorphine discontinuation (adjusted hazard ratio [aHR]: 0.72, 95% CI: 0.66-0.78). While person-days of psychostimulant use was associated with a lower likelihood of emergency admission for SUD-related events

(OR: 0.69, 95% CI: 0.63-0.76), we did not observe an association between psychostimulant treatment days and admission for specifically drug-related poisoning (OR: 0.95, 95% CI: 0.70-1.38).
Conclusions: The use of psychostimulants in pregnancy may be associated with improved buprenorphine retention as well as decreased acute care utilization for substance use disorder-related events, although other risks of psychostimulant use in pregnant people warrant further investigation.
Financial Support: This project was funded by R21 DA044744 (PI: Richard Grucza/Laura Bierut). Effort for some personnel was supported by grants T32 DA015035 (Kevin Xu, PI: Kathleen Bucholz, Jeremy Goldbach), but these grants did not fund the analyses of the Merative™ MarketScan® Multi-State Medicaid Database data performed by Dr. Xu.

Extended Observation of Reduced Methamphetamine Use With Bupropion and Naltrexone Treatment

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[1]University of California Los Angeles, [2]University of Texas Southwestern Medical Center, [3]The University of Texas Southwestern Medical Center, Department of Psychiatry, [4]University of Texas Southwestern Medical Center At Dallas
Select Drug Category Stimulants
Topic Treatment
Abstract Detail Clinical - Experimental
Abstract Category Original Research
Aim: A double-blind, two-stage, placebo-controlled trial of extended-release injectable naltrexone plus oral extended-release bupropion (BUP+NTX) for methamphetamine (MA) use disorder showed that BUP+NTX in the first 6 weeks of the trial was linked to superior increases in negative urine tests compared to placebo, but subsequent changes in weeks 7-12 was unknown. Therefore, this study aimed to estimate changes in testing MA-negative in those receiving BUP+NTX for the full 12 weeks of the study compared to placebo.
Methods: Piecewise mixed effects logistic regression was used to estimate change in odds of providing a negative urine test at twice weekly study visits over 12 weeks, comparing BUP+NTX to placebo. By trial design, a subset of the placebo group who did not show a response in stage 1 (weeks 1-6) was re-randomized 1:1 to either receive BUP+NTX or stay in placebo during stage 2 (weeks 7-12). For this analysis, to minimize any bias due to change in composition of the placebo group in stage 2, we simulated the subset of those re-randomized to BUP+NTX as if they had stayed in placebo in stage 2.
Results: Participants who received BUP+NTX in both stages showed additional increases in stage 2 in their probability of testing MA-negative (0.11; 95% CI [0.04, 0.19]). Over the full 12 weeks, the total increase in probability of testing MA-negative was 0.26 (95% CI [0.14, 0.38]) in those receiving BUP+NTX. In contrast, participants who received placebo in both stages increased in probability of testing MA-negative by 0.16 (95% CI [0.08, 0.24]) by week 12.
Conclusions: Analyses suggest continued treatment with BUP+NTX after 6 weeks is associated with additional reduction in MA use up to 12 weeks, warranting further investigation about the benefits of increased duration of BUP+NTX treatment for MA use disorder.
Financial Support: Supported by awards (UG1DA020024, K01DA051329, UG1DA013035, UG1DA040316, UG1DA013727, and UG1DA015815) from the National Institute on Drug Abuse (NIDA) of the National Institutes of Health; and by the Department of Health and Human Services under contract numbers HHSN271201500065C (Clinical Coordinating Center, the Emmes Company) and HHSN271201400028C (Data and Statistics Center, the Emmes Company). Alkermes provided Vivitrol (naltrexone for extended-release injectable suspension) and matched placebo free of charge for use in this trial under a written agreement with NIDA.

Late-Breaking Oral Session 2
Governor's Square 15

Differences in Coactivation Patterns in Chronic Nicotine Users

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Select Drug Category Nicotine/Tobacco
Topic Imaging
Abstract Detail Clinical - Experimental
Abstract Category Original Research
Aim: Nicotine dependence is associated with altered coordinated activity between brain regions, which can be measured using functional magnetic resonance imaging (fMRI) at rest. Most prior resting-state work used static approaches, which are not designed to capture time-varying patterns of functional coordination among distributed brain systems. This gap is relevant as networks transition from one state to another over time and such dynamic properties may provide essential features of large-scale network function in nicotine dependence.
Methods: 110 nicotine dependent individuals (61 female) and 110 matched healthy controls (60 female) underwent a 16-min resting state fMRI scan, on which coactivation pattern analysis was completed using 8 predefined brain states. Total time spent in state, average time spent in each state per entry, and the frequency of transitions into states were compared with two sample t-tests and corrected for multiple comparisons.
Results: Nicotine dependent individuals spent more time in and transitioned more frequently to the frontoinsular-default mode network (DMN) ($p<0.001$) and the occipital and sensory motor states ($p<0.001$) compared to healthy controls. In contrast, healthy controls spent more total time in the salience ($p=0.001$) and frontoparietal states ($p=0.02$), transitioned more frequently to the salience ($p<0.001$) and frontoparietal ($p=0.003$) states and persisted longer in the salience network state ($p=0.001$).
Conclusions: Compared to controls, nicotine dependent individuals spend more time in a frontoinsular-DMN state, which is relevant as spending more time in this state is associated with greater rumination. In addition, those who chronically smoke spent less time in the salience and frontoparietal states, which are involved in evaluating information to guide decision making. These findings suggest that chronic nicotine dependent individuals have temporal patterns of brain function that render such individuals more likely to engage in cognitions that can contribute to increased craving and reduce the control of drug-related behavior.
Financial Support: This research was supported by the Intramural Research Program of the NIH, NIDA

Using Biomarker Ratios to Distinguish Between Exclusive and Dual Use of Cigarettes, Smokeless Tobacco, and e-Cigarettes

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Select Drug Category Nicotine/Tobacco
Topic Behavioral Pharmacology
Abstract Detail Clinical - Epidemiology
Abstract Category Original Research
Aim: Biomarkers that distinguish between types of tobacco product use are vital to identifying potentially associated health effects, as well as to inform tobacco product reviews and regulatory actions. This study measured nicotelline and anatalline, minor tobacco alkaloids associated with tobacco smoke particulate matter, in urine biospecimens from US adults who exclusively use cigarettes, smokeless tobacco (SLT), or electronic nicotine delivery system (ENDS), as well as adults who use SLT + cigarettes or ENDS + cigarettes from Wave 1 of the PATH Study. We hypothesized that the ratio of these alkaloids, and/or their ratios with other biomarkers of tobacco exposure, would differentiate types of tobacco product use.
Methods: Nicotelline and anatalline were quantified by liquid chromatography tandem mass spectrometry. Receiver Operating Curve (ROC) characteristics of different biomarker ratios and Youden's J-index were used to determine the best threshold for distinguishing between use groups.
Results: The anatalline/nicotelline ratio by tobacco use group ranked highest to lowest: exclusive SLT (55.2 (95%CI: 47.2-64.5), dual SLT + cigarette (18.2 (95%CI: 13.2-25.1), exclusive cigarette (12.1 (95%CI: 10.3-14.1), dual ENDS + cigarette (10.0 (95%CI: 8.2-12.3), and exclusive ENDS (4.8 (95%CI: 3.6-6.4); $p < 0.001$). ROC analyses indicated the anatalline/nicotelline ratio was good at distinguishing between exclusive cigarette and SLT use (threshold= 2.9 (AUC= 0.90; Sensitivity= 89%, Specificity= 86%)), and exclusive

ENDS from SLT use (threshold= 2.6 (AUC= 0.90; Sensitivity 96%, Specificity= 76%)), but not exclusive cigarette from ENDS nor dual use from single product use. Ratios of nicotelline and other biomarkers had improved sensitivity and specificity for distinguishing exclusive cigarette and ENDS (e.g., Nicotelline/Cotinine ratio threshold= 2.5, (AUC= .84; Sensitivity= 91%, Specificity= 76%)) and exclusive SLT vs. dual SLT + cigarettes (Nicotelline/NNAL ratio threshold= .84 (AUC= .82; Sensitivity= 74%, Specificity= 81%)).
Conclusions: Anatalline and nicotelline can create biomarker ratios that distinguish between types of exclusive and dual tobacco product use.
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The Influence of Intraoperative Opioid Administration on Postoperative Pain and Opioid Requirements

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Select Drug Category Opiates/Opioids
Topic Tolerance/Dependence
Abstract Detail Clinical - Epidemiology
Abstract Category Original Research
Aim: Characterize the relationship between intraoperative opioid administration and postoperative pain and opioid requirements.
Methods: We conducted a retrospective cohort study of 61,250 adult patients who received non-cardiac surgery under general anesthesia at a quaternary care center between 2016 and 2020. The exposure variable was intraoperative fentanyl and intraoperative hydromorphone average effect site concentration. The primary study outcomes were maximal pain score during post-anesthesia care unit (PACU) stay and cumulative opioids administered in the PACU in morphine milligram equivalents (MME). Secondary outcomes included frequency of uncontrolled pain at 24 hours, new instances of chronic pain diagnosis, total opioid use at 24 hours and in-hospital, opioid prescriptions at 30, 90, and 180 postoperative days, frequency of new persistent opioid use, maximal pain score in the first 24 hours and in-hospital, and incidence of opioid related complications in PACU. We used multivariate propensity weighting to control for confounding and estimated the counterfactual difference in outcomes after administration of an additional 100 mcg fentanyl or 500 mcg hydromorphone intraoperatively.
Results: Increased intraoperative fentanyl and intraoperative hydromorphone were both associated with reduced maximum pain scores in the PACU. Both exposures were also associated with a reduced probability and reduced total dosage of opioid administration in the PACU. We found that increased fentanyl administration in particular was associated with lower frequency of uncontrolled pain, decreased chronic pain at 3-months, fewer opioid prescriptions at 30-, 90-, and 180-days, and decreased persistent opioid use, without significant increases in side effects.
Conclusions: Our results show that intraoperative opioid administration is significantly associated with short- and long-term effects on post-operative pain and opioid outcomes. Contrary to prevailing trends, reduced opioid administration during surgery may have the unintended consequence of increasing postoperative pain and opioid consumption. Our analysis suggests that significant improvements in long-term outcomes might be achieved by optimizing opioid administration during surgery.
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Incubation of Oxycodone Craving After Voluntary Abstinence is Associated With Increased Activity of Claustrum and Paraventricular Nucleus of Thalamus (PVT) Projections to Ventral Subiculum

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Select Drug Category Opiates/Opioids
Topic Behavior
Abstract Detail Preclinical - In Vivo
Abstract Category Original Research
Aim: We recently found a critical role of ventral subiculum (vSub) in incubation of oxycodone seeking after electric barrier-induced abstinence, a procedure mimicking human voluntary abstinence due to adverse consequences of drug seeking (Fredriksson et al. Sci Adv 2023). Here, we further characterized the role of vSub in incubation of oxycodone seeking by investigating projection-specific activation of vSub afferents using the activity marker Fos and the retrograde tracer cholera toxin B (CTb).
Methods: We trained Sprague-Dawley rats (n=22, 11 females) to self-administer oxycodone (0.1 mg/kg/infusion, 6-h/d) for 14 days. Next, we injected CTb (50 nl of 1% CTb) into vSub and then exposed the rats for 14 days to an electric barrier of increasing intensity (0.1 to 0.4 mA) near the drug-paired lever that caused voluntary abstinence. We tested the rats for relapse to oxycodone seeking without shock and drug on abstinence day 15 and immediately after testing anesthetized, perfused, and extracted their brains for Fos and CTb immunohistochemistry.
Results: We found that incubation of oxycodone seeking after electric barrier-induced abstinence was associated with increased Fos expression in anterior ($F[1,20]= 13.8$, $p=0.001$) and posterior ($F[1,20]= 17.6$, $p<0.001$) claustrum, and anterior ($F[1,20]= 6.0$, $p=0.023$) but not posterior ($F[1,20]= 0.55$, $p=0.47$) paraventricular thalamus (PVT) neurons projecting to vSub.
Conclusions: Incubation of oxycodone seeking after voluntary abstinence induced by adverse consequences of drug seeking is associated with activation of claustrum→vSub and anterior PVT→vSub projections. We currently analyze activation of additional projections to vSub (basolateral amygdala, medial septum, nucleus reuniens) and have begun to test the causal role of the claustrum→vSub projection in incubation of oxycodone seeking. We will present these data at the meeting.
Financial Support: This work was supported by NIDA/NIH.

When a Prophecy Comes True: Ethyleneoxynitazene as a 'Prophetic' Member of the Emerging Class of 2-Benzylbenzimidazole 'Nitazene' Synthetic Opioids

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Select Drug Category Opiates/Opioids
Topic Molecular Pharmacology
Abstract Detail Preclinical - In Vitro
Abstract Category Original Research
Aim: New synthetic opioids continue to emerge on recreational drug markets. Recently, opioids with a 2-benzylbenzimidazole core (‘nitazenes’, e.g. isotonitazene) have become increasingly prevalent, the potency of some members dwarfing that of fentanyl. The aim of our work is to in vitro and in vivo characterize existing, as well as 'prophetic' nitazenes, to allow risk prioritization based on structure activity relationships. As a case example, the pharmacological characterization of ethyleneoxynitazene, which we predicted to emerge, and which was first found in January 2023, will be presented.
Methods: In vitro pharmacological characterization (experiments performed in quintuplicate) encompassed assessment of mu opioid receptor (MOR) activation via a β-arrestin2 recruitment assay to derive the potency and efficacy, as well as radioligand binding assays performed in rat brain tissue. Pharmacodynamic effects were evaluated in male Sprague Dawley rats and included assessment of antinociceptive, cataleptic, and thermic effects.
Results: Radioligand binding assays revealed a Ki of 57.9 nM at MOR; only slightly higher than the Ki of etonitazene (38.4 nM), the most potent nitazene. Despite a similar affinity, ethyleneoxynitazene had a >100-fold lower potency in the MOR-β-arrestin2 recruitment assay (EC50 etonitazene 0.588 nM; ethyleneoxynitazene 70 nM). Also its efficacy (relative to the reference hydromorphone) was lower than that of etonitazene (Emax 187% vs. 254%). The strongly reduced MOR activation potential was also evident from the in vivo antinociception (mouse hot plate) assay, with an ED50 of 0.0223 mg/kg and 11.1 mg/kg for

etonitazene and ethyleneoxynitazene, repectively. The hypothermia and catalepsy assays revealed the same pattern.
Conclusions: The a priori availability of pharmacological (in vitro and in vivo) data by the time the 'prophetic' opioid ethyleneoxynitazene hit the recreational drug market allowed us to predict that, compared to several other nitazenes, this is not the opioid of highest concern. Similarly, pharmacological data for other 'prophetic' nitazenes are now readily available.
Financial Support: This work received financial support from the Intramural Research Program of the National Institute on Drug Abuse, National Institutes of Health, US, and from the Fund for Scientific Research, Flanders, Belgium.

Avoiding Naloxone-Induced Precipitated Withdrawal: A Procedure for Studying Opioid Negative Reinforcement in Rats

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Select Drug Category Opiates/Opioids
Topic Tolerance/Dependence
Abstract Detail Preclinical - In Vivo
Abstract Category Original Research
Aim: Operant negative reinforcement (withdrawal avoidance) plays a key role in human opioid addiction. Preclinical rat models of operant withdrawal avoidance do not exist. We adapted for rats a primate model of opioid negative reinforcement (Downs and Woods. Pharmacol Rev. 1975).
Methods: In Exp. 1, we trained rats (n= 39,19 females) to lever-press to escape mild footshocks to screen for operant negative reinforcement. Next, we catheterized them and implanted minipumps containing methadone (10 mg/kg/day). We then exposed the rats to 4 warning cues followed by naloxone infusions (20 µg/kg, i.v) to induce opioid-withdrawal. Next, we trained them on an operant procedure for naloxone avoidance/escape. Each trial started with the onset of the previously paired opioid-withdrawal cue. After 20-s, a lever extended and an infusion of a low naloxone dose (1 µg/kg) or saline infusion began; a lever-press during an 11-s window would terminate the withdrawal-paired cue and infusion. In this procedure, the rats lever-press to escape naloxone infusions, where consecutive failed escapes cause precipitated-withdrawal; thus, the rats lever-press to actively avoid naloxone-precipitated withdrawal. In Exp. 2, we trained rats (n=9, 4 females) to lever-press to actively avoid mild footshocks. We then trained the rats on the same naloxone avoidance/escape procedure of Exp 1.
Results: In Exp. 1, the rats learned to lever-press to escape mild footshocks but not naloxone-precipitated withdrawal. Preliminary data from Exp. 2, where rats were pretrained on the shock avoidance procedure, showed higher lever-presses to escape naloxone injections in methadone-dependent rats (Group [saline, methadone] x Session [1-to-10], F[9,63], p=0.001).
Conclusions: We introduce an operant negative reinforcement procedure where opioid-dependent rats lever-press to avoid and escape opioid withdrawal after shock avoidance (but not shock escape) pretraining. Pending independent replications, the procedure can be used to study mechanisms of operant negative reinforcement in opioid-dependent rats.
Financial Support: None

Intranasal Human Abuse Potential of PF614: A Novel 'Next Generation' Trypsin Activated Abuse Protected (TAAP) Opioid

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Select Drug Category Opiates/Opioids
Topic Other
Abstract Detail Clinical - Experimental
Abstract Category Original Research
Aim: Abuse of opioid medications continues to be a public health crisis despite the approval of 'Abuse Deterrent' products. TAAP prodrugs represent novel products that are inactive until swallowed and activated

by trypsin in the small intestine. In previous studies, a 100 mg dose of TAAP oxycodone, PF614, was shown to be bioequivalent to OxyContin 40 mg, but with a significantly longer (12 hr versus 4.4 hr respectively) half-life. The Aim of the intranasal human abuse potential (HAP) study was to assess the safety, pharmacokinetics, and abuse potential of intranasal PF614 compared to oxycodone HCl and placebo.
Methods: In the intranasal HAP study, PF614 100 mg was compared to 40 mg crushed IR oxycodone HCl and placebo (n=25) in a 3-way double-blind, randomized, crossover trial. All drugs were administered as powder via intranasal cannula from amber dosing vials. All subjects were pre-qualified to recognize opioid exposure using validated visual analogue scales (VAS). 68 Subjects were screened; 43 enrolled into the qualification phase; 27 were randomized, and 25 met the criteria for the modified completer population (MCP). Key endpoints of 'Drug Liking' and 'Take Drug Again' were evaluated up to 24 hr after dosing.
Results: In the intranasal HAP study, PF614 produced significantly lower peak "Drug Liking" (Emax) score compared oxycodone ($p<0.0001$) using the full MCP. Similarly, the first period analysis of initial impressions ("Overall Drug Liking") showed significantly less liking in the PF614 group (n=8) vs. crushed IR oxycodone (n=9) ($p=0.0109$). The "Take Drug Again" score for IN PF614 was significantly less than that of oxycodone ($p<0.0001$) in the MCP.
Conclusions: Intranasal PF614 showed significantly less abuse potential than IR oxycodone. PF614 could represent a new class of 'Next Generation of Opioids' that require trypsin activation and cannot be manipulated to release an immediate-onset drug load.
Financial Support: Supported by: Ensysce Biosciences Inc.

Role of Piriform Cortex and it's Afferent Projections in Relapse to Fentanyl Seeking After Food Choice-Induced Voluntary Abstinence

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Select Drug Category Opiates/Opioids
Topic Neurobiology/Neuroscience
Abstract Detail Preclinical - In Vivo
Abstract Category Original Research
Aim: We previously showed a role of piriform cortex (Pir) in relapse to fentanyl seeking after food choice-induced voluntary abstinence, a procedure that mimics abstinence due to availability of alternative non-drug rewards. Here, we used this model to further study the role of Pir and its afferent projections in fentanyl relapse.
Methods: We trained male and female rats to self-administer palatable food pellets for 6 days (6 h/day) and fentanyl (2.5 µg/kg/infusion, i.v.) for 12 days (6 h/day). We assessed relapse to fentanyl seeking after 12 voluntary abstinence sessions, achieved through a discrete choice procedure between fentanyl and palatable food (20 trials/session). We determined projection-specific activation of Pir afferents during fentanyl relapse with Fos plus the retrograde tracer cholera toxin B (injected into Pir, n=5-6 per group). We then used an anatomical disconnection procedure to determine the causal role of AI-to-Pir (n=9-14 per group) and PL-to-Pir projections (n=13-15 per group) in fentanyl relapse. We analyzed the data with repeated-measures or mixed-factorial ANOVAs using IBM SPSS Statistics.
Results: Fentanyl relapse was associated with increased Fos expression in anterior insular cortex (AI) and prelimbic cortex (PL) neurons projecting to Pir ($p<0.05$). Contralateral but not ipsilateral disconnection of AI-to-Pir projections decreased fentanyl relapse ($p=0.01$) but not reacquisition of fentanyl self-administration ($p=0.28$). In contrast, contralateral but not ipsilateral disconnection of PL-to-Pir projections decreased reacquisition ($p=0.04$) but not relapse ($p=0.85$).
Conclusions: Results demonstrate that AI-to-Pir and PL-to-Pir projections play dissociable roles in non-reinforced relapse to fentanyl seeking versus reacquisition of fentanyl self-administration after food choice-induced voluntary abstinence.
Financial Support: This research was supported by funds to the NIDA Intramural Research Program.

Material Hardship and Encampment Relocation Among Unhoused People who Use Drugs: Confirmatory Factor Analysis and Structural Equation Modeling of a Scale Measure

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Select Drug Category Opiates/Opioids
Topic Harm Reduction
Abstract Detail Other
Abstract Category Original Research
Aim: Unhoused individuals experiencing material hardship have been increasingly subject to anti-camping policies resulting in forced and coerced displacement. In this study we examine internal validity and reliability of a new measure of material hardship among unhoused individuals, specifically among people who use opioids (PWUO). We examine the association between relocation events and this novel measure of material hardship.
Methods: Data was collected from an ongoing prospective cohort study of people who use opioids (PWUO), between 2020 and 2022 in Los Angeles, California and Denver, Colorado. Community recruited PWUO completed surveys at baseline, three months, and six months (n = 429). We used four baseline items (four-point ordinal scales) examining access to material resources in confirmatory factor analysis (CFA) to create a scale measuring material hardship. Structural equation modeling (SEM) was used to explore the association between being unhoused and displaced in the past three months (never, monthly, weekly, daily) and mean material hardship score.
Results: All four items of difficulty accessing food, clothing, showers, and restrooms, loaded well (> 0.7) onto a single latent factor we termed Hardship (range = 1 – 4) where a higher score indicates worse hardship. Fit statistics indicated good model fit (RMSEA = 0.034, 95% CI = 0.000 – 0.139; SRMR = 0.009). Coefficient alpha (0.88) and omega (0.76) values indicated good internal reliability. In SEM, after including demographic covariates, a one-category increase in displacement frequency was associated with a 0.452-point increase in mean Hardship.
Conclusions: Our Hardship scale showed good internal validity and reliability (data not shown). We found that increased mean Hardship score was associated with more frequent relocation when living outdoors, irrespective of demographic factors. As the crisis of unsheltered houselessness among PWUD in the US continues to grow, it appears that the policy of displacement negatively impacts well-being among PWUO.
Financial Support: NIH (F31-DA054763, R01-DA0460469)

Predictive Relationship Between Different Timescales of Opioid Craving and Opioid Use

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Select Drug Category Opiates/Opioids
Topic Substance Use Disorder
Abstract Detail Clinical - Experimental
Abstract Category Original Research
Aim: Craving, or the intense, specific desire for drugs, is robustly associated with drug use and relapse. However, little is known about the timescale of the predictive relationship between craving and drug use. We aimed to examine this relationship in a longitudinal study of individuals enrolled in medications for opioid use disorder (MOUD) treatment.
Methods: At each longitudinal session (mean=5.3/person, SD=3.58, range: 1-15), participants (N=120) reported on their past-week opioid use, provided a sample for urinalysis, and reported on their opioid craving over three timescales: in-the-moment (current urge and ability to resist opioid use), past 24 hours (intensity, frequency, and length of time spent craving, and number of cravings), and past week (average craving). We used repeated-measures correlation analyses and logistic mixed models to test our hypotheses of both a shared craving association across timescales (at session t) and also predictive relationships between craving (t) and future opioid use (between t and t+1), considering past-week use (t).
Results: Craving reports correlated moderately to strongly with each other across timescales (mean R=0.63, range: 0.32-0.93). All were also significantly elevated following past-week opioid use ($b>0.20$, $p<0.0015$).

By contrast, prospective relationships between craving and future opioid use differed somewhat by timescale and control for past-week use: strongest effects were observed for person-mean level craving at the past-week timescale ($b=2.49$, $p<0.001$; with past-week use in model: $b=0.53$, $p=0.018$), then past 24 hours ($b=1.98$, $p<0.001$; $b=0.42$, $p=0.022$), with weakest effects observed for in-the-moment ($b=1.48$, $p=0.018$; $b=0.24$, $p=0.076$). There were no consistent relationships with session-to-session changes in craving.
Conclusions: Higher average craving, especially when assessed over longer retrospective intervals, significantly predicts opioid use. Thus, rather than shorter-term changes in craving, an elevated trait-like craving experience may particularly predispose individuals to reuse. Further work is needed to better understand and inform measurement of the clinical phenomenology of craving for treatment targeting.
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