POSTER SESSION **Thursday, October 17, 2024**

	Room 1: Immune system / Inflammation / HIV
	Moderator 1: Jennifer Iudicello, PhD, Associate Professor of Psychiatry, UCSD
Pacific Time	**Moderator 2:** J. Adam Fields, PhD, Associate Professor of Psychiatry, UCSD
12:05-12:14	**Rogers, Jeff:** Recent Cannabis Use Moderates the Association Between Methamphetamine Use and Increased Markers of Inflammatory and Immune Processes
12:15-12:24	**Behling-Hess, Caroline:** The Impact of Cannabis on Immune Checkpoint Inhibitor Therapy: A systematic Review of Immunomodulatory Effects of Cannabis in Patients With and Without Cancer
12:25-12:34	**Vemuri, Sunitha:** Delta-9-Tetrahydrocannabinol Produces Consistent Physiological and Motivational Effects in HIV-1 Transgenic Rats Relative to Their Controls
12:35-12:44	**Avalos, Bryant:** Chronicity of Cannabis Use Modulates Disrupted Immunomodulatory Role of TREM2 in HIV
12:45-12:54	**Tomer, Shallu:** Impact of Cannabinoids on Interferon-Stimulated Gene Expression and HIV Infection in Macrophages
	Room 2: Health, safety, and cannabis
	Moderator 1: Mariana Cherner, PhD, Professor of Psychiatry, UC San Diego
	Moderator 2: Rudy Ortiz, PhD, Professor of Molecular & Cell Biology, UC Merced
12:05-12:14	**Mastropietro, Kyle:** Probing the Relationship Between Cannabis Users' Sex and Subjective Cannabis Intoxication in Relation to Cannabis Use Patterns and Post-Smoking Blood THC Concentrations
12:15-12:24	**Rattigan, Jake:** The Accuracy of Cannabis Users' Expectations of Drug Effects on Driving
12:25-12:34	**de Oliveria, André:** Medical Cannabis for Several Health Conditions: A Systematic Review and Meta-Analysis of Clinical Trials
12:35-12:44	**Yafai, Sherry:** State of Medical Cannabis in California
12:45-12:54	**Ayers, Chelsea:** Systematically Testing the Evidence on Marijuana (STEM)

	Room 3: Brain, nervous system, and neuropsychology
	Moderator 1: Arpi Minassian, PhD, Professor of Psychiatry, UCSD
	Moderator 2: Giordano de Guglielmo, PhD, Assistant Professor of Psychiatry, UCSD
12:05-12:14	**Sengupta, Arnab:** Effects of Psychotomimetic Doses of Δ9-THC on EEG Measures of Excitatory-Inhibitory Balance and its Relationship to Neural Noise
12:15-12:24	**Peek, Elizabeth:** A Preliminary Analysis of the Effects of Cannabis Use and Bipolar Disorder on Performance in the Neuropsychological Evaluation of the UPSA (NEUPSA)
12:25-12:34	**Rogers, Sophia:** Innovative Methods for Prenatal THC Exposure: Vaping Inhalation Chamber and Metabolite Quantification in Prairie Voles and Rats
12:35-12:44	**Rodrigues, Akeesha / Alayoubi, Myra:** Does the Terpene Myrcene Elicit Tetrad Effects Typical of CB1 Receptor Agonists?
12:45-12:54	**Rosberg, Holden:** Cannabis Use, Bipolar Disorder, and Exploratory Behavior in the Human Behavioral Pattern Monitor: A Preliminary Analysis
	Room 4: Innovative approaches and novel findings in cannabinoid science
	Moderator 1: Nicholas Dipatrizio, PhD, Professor of Biomedical Sciences, UC Riverside
	Moderator 2: Cecilia Marcondes, PhD, Professor of Neuroimmunology, San Diego Biomedical Research Institute
12:05-12:14	**Bilkei-Gorzo, Andras:** Shorter Life Span, Accelerated Frailty Development and Disturbed Insulin-Like Growth Factor Signaling in Cannabinoid Receptor Type-1 Knockout Mice
12:15-12:24	**Scialdone, Mark:** Hydrogenation of Phytocannabinoids
12:25-12:34	**Alvarez, Camila:** The Role of the Gut-Brain Endocannabinoid System in Food Reward
12:35-12:44	**Olmos, Martin:** The Impact of Cannabis Exposure on Gut Barrier Function in Health and Disease
12:45-12:54	**Ayoub, Samanta:** Mania-relevant Hyperexploration is Attenuated by Acute Cannabinoid-1 Receptor Blockade in Mice

The Role of the Gut-Brain Endocannabinoid System in Food Reward

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Background: The obesity epidemic is largely driven by overeating of high-fat and high-sugar diets combined with a sedentary lifestyle. Dysregulation of several neural and molecular pathways contribute to obesity and overeating, including gut-brain endocannabinoid (eCB) signaling. For example, our lab reported that mice display a strong preference for a Western-style diet (WD, high fat and sucrose) when compared to a standard rodent chow (SD, low fat and no sucrose), and this effect is blocked by global pharmacological inhibition of cannabinoid type-1 receptors (CB1Rs). Moreover, mice that conditionally lack CB1Rs selectively in the intestinal epithelium also display no preferences for WD, which suggests that CB1Rs in these cells are required for acute WD preferences. It is largely unknown, however, if gut-brain eCB signaling recruits brain reward pathways in these processes (i.e., dopamine control of motivated behavior).

Methods: In order to investigate this possibility, we recorded dopamine activity during an acute dietary preference test in mice used a virally-mediated, genetically-encoded, fluorescent dopamine sensor (AAV-hSynGRAB_DA2m) that is expressed in the nucleus accumbens. On the day of testing, mice were administered the peripherally-restricted CB1R neutral antagonist, AM6545 (10 mg per kg), and in vivo dopamine signaling was recorded during a two-hour preference test for WD or SD.

Results: Vehicle-treated control mice displayed large preferences for WD when compared to SD. In contrast to vehicle, mice treated with AM6545 had significant reductions in preferences for WD when compared to SD. Moreover, vehicle-treated mice displayed a persistent increase in dopamine activity when accessing the preferred WD, an effect that was attenuated in mice treated with AM6545.

Conclusions: These studies suggest that preferences for high-energy palatable foods, and associated dopaminergic signaling in the nucleus accumbens, are controlled by a mechanism that includes eCB signaling in the periphery. Roles for CB1Rs in the intestinal epithelium in the gut-brain control of food reward and motivated behavior are currently under investigation.

Chronicity of Cannabis Use Modulates Disrupted Immunomodulatory Role of TREM2 in HIV

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Background: Triggering Receptor Expressed in Myeloid Cells 2 (TREM2) serves a critical anti-inflammatory role in the brain. Cannabis use in people with HIV (PWH) is associated with lower inflammation and reduced neurocognitive impairment (NCI). We hypothesize that TREM2 dysfunction mediates HIV neuropathogenesis and cannabinoids found in cannabis, like cannabidiol (CBD), are neuroprotective in PWH by inducing TREM2 pathway activation.

Methods: To test if cannabis use activates the TREM2 pathway in PWH, we performed gene expression analyses using RT-qPCR and RNA-sequencing on monocyte-derived macrophages (MDMs) generated from PWH with the following cannabis use patters: 1) naïve; 2) moderate; and 3) daily use. To assess differences in TREM2 function, MDMs were treated with IL1β, CBD, or CBD plus IL1β and soluble TREM2 (sTREM2) levels were measured via ELISA.

Results: TREM2 mRNA levels increased with age in people without HIV (PWoH) but not PWH. CBD treatment increased TREM2 mRNA expression in the presence of IL1B and significantly decreased soluble TREM2 in MDMs. Additionally, TREM2 gene transcripts were higher in CBD-treated MDMs compared to IL1β treatment. RNA-sequencing and RT-qPCR data revealed gene expression patterns that suggest cannabis use in PWH is associated with restored expression of immunomodulatory genes, including upregulation of genes like *CHIT1* and *SMAD3* and downregulation of *TREM1* and *VSIG4*.

Conclusions: These findings suggest changes in TREM2 expression associated with HIV infection are modulated by cannabis and CBD. Additionally, cannabis use in PWH impacts immunomodulatory gene expression that could be downstream of TREM2 activation which may offer insights for therapeutic strategies in PWH. It remains unclear if other cannabis-derived compounds can also influence TREM2-mediated processes. Additional research is required to understand how cannabis influences TREM2-related pathways in the context of HIV-associated neuroinflammation.

Systematically Testing the Evidence on Marijuana (STEM)

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Background: With continuing legalization, more patients are using or interested in using cannabis. Meanwhile, many clinicians do not discuss the health effects of cannabis and most patients source this information from elsewhere (e.g., internet, cannabis dispensaries). Limited evidence regarding cannabis health effects (e.g., relatively few randomized controlled trials, lack of standard measures), and a rapidly-changing research and policy landscape, leave clinicians without definitive guidance on how to counsel patients, yet they need to be prepared to have these discussions.

Methods: The Systematically Testing the Evidence on Marijuana (STEM) project is an independent, methodologically rigorous, and up-to-date resource (CannabisEvidence.org) that synthesizes what is known from research and what is left to learn about the health effects of cannabis. Using best-practice approaches to living systematic reviews, and guided by a technical expert panel comprised of individuals with cannabis-related clinical and research expertise, STEM aims to: 1) Empower clinicians to have evidence-based discussions about cannabis use with patients. 2) Identify research gaps and highlight ongoing research to help researchers design high-yield studies that advance the field of clinical cannabis research.

Results: Since the launch of the website in January 2022 STEM has: 1) Maintained 6 living systematic reviews. Each review features a full report, high-level summary, and a visual abstract so that readers can find the level of detail they need. 2) Developed 13 clinical briefs, on topics ranging from “patient experiences when visiting dispensaries” to “cannabis and sleep”. 3) Garnered < 49,000 page views by < 14,000 unique users 4) Provided a variety of other resources related to cannabis and health pertinent to researchers and clinicians, including: basic cannabis information (e.g., terminology, pharmacology),a searchable database of ongoing studies of cannabis-related research, guidance on conduct of cannabis-related research in the US, an interactive map of cannabis legal status and key cannabis use statistics by US state, an updated collection of curated high-quality news articles relevant to our audience, continuing medical education credits available to clinicians after reviewing the website.

Conclusions: STEM is an innovative approach to help address gaps in knowledge and resources on the health effects of cannabis for clinicians and researchers. The STEM team is continuing to seek ways to further engage with researchers and clinicians through ongoing studies and collaborations with the goal of supporting clinicians to have evidence-based discussions about cannabis use with patients that support shared decision-making and improve patient outcomes.

Mania-relevant Hyperexploration is Attenuated by Acute Cannabinoid-1 Receptor Blockade in Mice

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Background: People with bipolar mania (BM) exhibit hyperexploratory behaviors and dysregulated dopamine function, including reductions in expression of the dopamine transporter (DAT). In rodents DAT inhibition reliably recreates such BM-relevant hyperexploration, which can be attenuated by BM medications (e.g., lithium), thus exhibiting predictive pharmacological validity. Given the adverse side-effects associated with treatments prescribed for BM, novel treatment options are needed. The endocannabinoid (eCB) system is also dysregulated in BM and is a promising target given its neuromodulatory role in dopamine signaling. Here, we examined the impact of altering eCB receptor activity via behavioral pharmacology on hyperexploration induced by pharmacological DAT inhibition by GBR12909.

Methods: Female and male C57BL/6J mice were tested in the behavioral pattern monitor (BPM) for 45 min once per week following systemic pretreatment with the eCB system modulators AM251 (cannabinoid-1 receptor antagonist [CB_1R], 1–3 mg/kg), AM630 (cannabinoid-2 receptor antagonist [CB_2R], 1–10 mg/kg), THC (0.3–3mg/kg), or CBD (0.3–3 mg/kg), alone, or in combination with the DAT inhibitor GBR 12909 (GBR; 0, 16 mg/kg). Repeated-measures ANOVAs were conducted to assess the main effects and interactions of pretreatments and GBR exposure on locomotor activity (distance travelled) and specific exploration (rearing) across time-binned data.

Results: GBR 12909 recreated the BM-relevant BPM hyperexploratory profile (increased locomotor activity and specific exploration). Pretreatment with the CB_1R antagonist AM251 (3 mg/kg) reduced distance travelled, but not rearing, in GBR-treated animals, with no effect in controls, specifically in time bins 2 and 3 (GBR*Pretreatment*Time: $F(6,238)=2.64$, $p=0.017$]. Pretreatment with acute AM630, THC, or CBD did not alter GBR-induced effects, though high-dose THC decreased locomotor and exploratory behavior of GBR-treated and control groups.

Conclusions: These data support: 1) reducing CB_1R, but not CB_2R, receptor function attenuates BM-relevant hyperlocomotion without attenuating BM-relevant increased specific exploration; 2) DAT function altered the role of the cannabinoid-1 receptor in locomotor patterns; and 3) neither THC nor CBD selectively affected BM-relevant hyperexploration. Thus, direct targeting of the cannabinoid-1 receptor may be suitable for attenuating BM-relevant hyperactivity.

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The Impact of Cannabis on Immune Checkpoint Inhibitor Therapy: A systematic Review of Immunomodulatory Effects of Cannabis in Patients With and Without Cancer

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Background: Patients with cancer use cannabis to control symptoms related to cancer or cancer-directed therapies with significant palliative benefits. As the use of immune checkpoint inhibitors (ICIs) for cancer therapy becomes more widespread, there is concern about potential interactions between ICIs and cannabis. *In vitro* studies suggest that cannabis leads to immunosuppression, which could negatively affect the function of ICIs designed to upregulate T-cell mediated killing of cancer cells. However, only a few clinical studies have investigated this relationship. The goal of this review is to synthesize reported immunomodulatory effects of cannabis in clinical studies of patients with and without cancer in order to better understand whether these *in vitro* findings translate to the clinical space.

Methods: A database search was conducted through Ovid Medline to identify relevant articles. Clinical studies investigating the relationship between cannabis use in humans and the immune system were included. *In vitro* reports, animal studies, and case studies were excluded. Information pertaining to immune changes with cannabis exposure was abstracted. Studies were graded based on three criteria with randomized trials using measured cannabinoid doses and assessing laboratory immune-related markers receiving the highest scores.

Results: Forty studies met inclusion criteria, including 9 randomized, placebo-controlled clinical trials. Analysis of immune-related markers demonstrated no change in cytokines, T cell counts, and CRP in most studies with cannabis exposure, including among studies with higher quality of evidence ratings. Among patients with autoimmune diseases, cannabis use showed improvements in clinical symptoms even while objective laboratory immune markers remained unchanged. There was significant variation in the THC and CBD doses utilized making comparisons among studies difficult.

Conclusions: We did not find evidence of meaningful changes in immune parameters with cannabis use in the clinical setting across multiple diseases. In particular, immune markers relevant to the cytotoxic branch of the immune system necessary for ICI benefit did not appear to be associated with cannabis use. This evidence may provide some reassurance to patients with cancer and their oncologists contemplating concomitant cannabis use with ICI, however, additional well-controlled prospective studies are warranted in this setting.

Shorter Life Span, Accelerated Frailty Development and Disturbed Insulin-Like Growth Factor Signalling in Cannabinoid Receptor Type-1 Knockout Mice

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Background: Cannabinoid receptor type-1 (Cnr1) signalling declines with age. This is because both its expression and G-protein coupling are lower in old individuals than in young ones. This decline may contribute to the ageing process, as Cnr1 activity influences several hallmarks of ageing. Indeed, previous studies have shown that mice with a genetic deletion of Cnr1 (Cnr1-/-) exhibit an early onset of brain ageing. However, it is not yet clear whether Cnr1 activity influences life span and the pace of bodily ageing. In this study, we demonstrate that the life span of the Cnr1-/- mice is shorter and they show an accelerated frailty development, reduced insulin-like growth factor 1 (IGF-1) signalling and lower gonadotropin-releasing hormone (GnRH) production.

Methods: We conducted a longitudinal study to test the lifespan and frailty development of a colony of male and female $Cnr1^{-/-}$, $Cnr1^{+/-}$ and $Cnr1^{+/+}$ wild-type mice in our animal facility. We isolated blood plasma and hypothalamus from a separate group of 3- and 12-month-old wild-type and $Cnr1^{-/-}$ mice. We then compared the hypothalamic expression of elements of IGF signalling, growth hormone (GH) and GnRH production between the genotypes, as well as the blood plasma IGF-1 levels.

Results: Comparison of survival curves revealed that the median survival time of $Cnr1^{-/-}$ mice was lower than that of $Cnr1^{+/+}$ wild-type or $Cnr1^{+/-}$ mice. Frailty developed earlier and was more intense in both knockout and heterozygous animals than in their wild-type siblings. We therefore next asked whether IGF-1 signalling is altered in $Cnr1^{-/-}$ mice, given that the blood plasma level of insulin-like growth factor-1 (IGF-1) strongly influences the pace of bodily ageing. We were surprised to find that $Cnr1^{-/-}$ mice had reduced hypothalamic expression of GHRH and lower IGF-1 plasma levels – thus reduced IGF-1 signalling. Furthermore, we observed a reduced expression of elements of IGF-1 receptor signalling in the hypothalamus of knockout animals. We proceeded to control the expression of GnRH in two age groups of wild-type animals, given that it is well-established that reduced GnRH production leads to accelerated ageing. Our results confirmed that both age groups of $Cnr1^{-/-}$ mice exhibited lower GnRH expression in their hypothalamus.

Conclusions: Our present study shows that reduced CB1 receptor activity accelerates physical ageing by reducing GnRH production and disrupting IGF-1 signalling. We hypothesise that the activity of the cannabinoid system influences the rate of brain and body ageing.

Probing the Relationship Between Cannabis Users' Sex and Subjective Cannabis Intoxication in Relation to Cannabis Use Patterns and Post-Smoking Blood THC Concentrations

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Background: Human studies exploring sex differences after THC exposure are limited. While some studies found that females report greater intoxication than males, including at lower whole blood THC concentrations, others found indistinguishable self-reported intoxication after smoking similar amounts. The current study expands this work to examine whether males and females, closely matched on cannabis use variables, demonstrate sex differences in residual whole blood THC/metabolites, subjective intoxication, and driving performance following acute cannabis consumption.

Methods: This study was part of a randomized clinical trial. Participants smoked *ad libitum* THC cigarettes then completed driving simulations, blood draws, and self-reported intoxication measures. The main outcomes were change from pre-smoking baseline in Composite Drive Score (CDS; global measure of driving performance), whole blood THC, 11-OH-THC, and THC-COOH levels (ng/mL); the ratio of post-smoking ng of blood THC per kg of body weight; and subjective ratings of "highness" (0=not at all, 100=extremely). Analyses focused on participants receiving active THC. Males/females were matched on 1) estimated cannabis exposure (g) in the last 6 months (24M, 24F) or 2) post-smoking whole blood THC concentrations (23M, 23F).

Results: When matched on THC exposure in the past 6 months (M=46g; p=0.99), there were no sex differences in any cannabinoid/metabolite concentrations at baseline (ps>0.83) or post-smoking (ps>0.72), nor in ng of blood THC per kg of body weight post-smoking (p=0.53). There were no differences in CDS change from pre-to-post-smoking (p=0.26) or subjective "highness" (p=0.53). When matched on whole blood THC concentrations post-smoking (M=34ng/mL, p=0.99), no differences were found in CDS change from baseline (p=0.81), cannabinoid/metabolite concentrations (ps>0.25), subjective "highness" (p=0.56), nor ng of blood THC per kg of body weight (p=0.55). For both analyses, males/females did not differ in BMI (ps>0.7).

Conclusions: Previous studies finding sex differences were limited in not matching males/females on variables that may predict subjective responses to THC. We found that male/female cannabis users, once well-matched on use history, had no differences in cannabinoid concentrations following ~5 days of abstinence, suggesting no biological differences in residual effects. We also find no differences in post-smoking driving performance, subjective highness, nor whole blood THC/metabolite concentrations, indicating no biological differences in acute THC response. This improves upon previous research by matching participants over a wider range of use intensity variables, although the small sample size and focus on intoxication after only smoked cannabis precludes definitive conclusions.

Medical Cannabis for Several Health Conditions: A Systematic Review and Meta-Analysis of Clinical Trials

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Background: Cannabis spp. has more than 100 compounds, such as cannabidiol (CBD) and Δ-9-tetrahydrocannabinol (THC). Although there are historical records of its medical use since ancient times, it was only in the 19th century that it became widespread in western societies. Food and Drug Administration (FDA) has registered few cannabis-based products, even though the medical indications of phytocannabinoids are diverse. There is great therapeutic potential in these products, but the wide range of clinical conditions that can benefit from the use of medical cannabis is not systematized enough in the literature. The objectives are to evaluate the feasibility, safety, and efficacy of the medical cannabis use in the treatment of several health conditions compared to placebo or medications already used for the disorders and update a systematic review and meta-analysis published in 2015.

Methods: The proposal is a systematic review and meta-analysis, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) system and documented in the International Prospective Register of Systematic Reviews (PROSPERO). Every study will be grouped according to clinical presentation or type of disease (neurodevelopmental disorders; neurodegenerative disorders; autoimmune diseases; and neuropsychiatric disorders). Clinical studies will be independently selected by two reviewers, in English only, and the search period will be until 2023. Inclusion criteria are: randomized experimental clinical trials in humans (double-blind, open-label, or single-dose) that have tested cannabis (THC or/and CBD or/and any other cannabis product) vs. placebo, or vs. any other medications. Additionally, the exclusion criteria are: preclinical trials with cannabis in animal models, observational studies, literature reviews or studies with results from patient and family questionnaires. Risk of bias will be assessed according to the Jadad scale and analyses will be performed in the Review Manager program.

Results: We expect that there will be a greater number of studies published after 2014 and that autoimmune diseases and neurodevelopmental disorders will be the most prevalent in terms of the number of investigations. Regarding the level of evidence, it is known that the disorders for which the FDA has approved the clinical use have better outcomes when using cannabis-based products.

Conclusions: Cannabis-based products should be a therapeutic option for the treatment of several diseases and studies such as the proposal presented can guide clinical decisions based on the most robust level of evidence.

The Impact of Cannabis Exposure on Gut Barrier Function in Health and Disease

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Background: The endocannabinoid (eCB) system is a lipid-derived signaling pathway that controls food intake, energy homeostasis, and reward. This system is expressed throughout the body, including in the gastrointestinal tract, where it becomes dysregulated in diet-induced obesity (DIO) and may participate in gut barrier function; however, it is unclear if the eCB system exerts a protective or detrimental role in gut function. Indeed, studies from our lab suggest that the eCB system in intestinal epithelial cells controls gut barrier function, and associated inflammation, and its activity exerts a protective influence during diet-induced obesity in mice. Moreover, studies suggest that activating the eCB system with chemicals found in cannabis prevents colitis and increases colonic barrier integrity. Conversely, other studies have shown that pharmacological activation of cannabinoid receptors in lean mice led to an increase in plasma levels of lipopolysaccharide, which suggests a compromised gut barrier function.

Methods: Given these discrepancies as to the protective or detrimental roles for the eCB system in gut health and function, we now are examining the impact of THC (i.e., the primary intoxicating chemical in cannabis), as well as whole cannabis extracts, on gut barrier function in a diet-induced obese mouse model that displays a mild phenotype of disrupted barrier function.

Results: Preliminary results highlight a largely protective effect for chemicals in the obese model that requires cannabinoid CB1 receptors in the intestinal epithelium in a sex-dependent manner.

Conclusions: The knowledge gained from these investigations will provide critical insights into the therapeutic potential of cannabis as a treatment for diseases that affect gastrointestinal barrier function.

A Preliminary Analysis of the Effects of Cannabis Use and Bipolar Disorder on Performance in the Neuropsychological Evaluation of the UPSA (NEUPSA).

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Background: The UCSD Performance Skills Assessment (UPSA) is a well-established performance instrument created to evaluate functional outcomes. We applied a neuropsychological framework to the UPSA and created the Neuropsychological Evaluation of the UPSA (NEUPSA), assessing the cognitive processes that underlie the functional tasks in the UPSA. The study aimed to compare the executive function and attention components of the NEUPSA with validated computerized cognitive assessments and test associations between cannabis use (CU), bipolar disorder (BD) and NEUPSA performance.

Methods: We recruited 91 participants, including participants with a BD diagnosis (BD) and healthy comparison participants (HC), who either regularly use cannabis (+CU) or do not use cannabis. Participants completed the UPSA, 5-Choice CPT (5CCPT), which assesses sustained attention, and the Iowa Gambling Task (IGT), which assesses risky decision making. We employed a Spearman's correlation analysis to test associations between NEUPSA attention and executive function sub-scores and 5CCPT and IGT performance respectively. We performed a 2-way ANOVA to test for interactions and main effects of CU and BD, and pairwise t-tests to test for differences between the 4 comparison groups (HC+CU n=26, BD+CU n=26, BD n=13, HC n=26).

Results: NEUPSA attention sub-scores were positively correlated with 5CCPT hit rate unmasked scores ($r=0.24$, $p=0.03$) and 5CCPT d-prime unmasked scores ($r=0.24$, $p=0.02$). NEUPSA executive functioning sub-scores were positively correlated with IGT scores ($r=0.26$, $p=0.02$). There was a significant interaction between CU and BD on NEUPSA Executive Functioning sub-scores, ($F(1, 87) = 6.415$, $p = 0.013$, partial $\eta 2 = 0.069$), such that HC participants had significantly better performance compared to HC+CU (p-0.050) and BD participants ($p=0.015$). There was no significant interaction between CU and BD on the NEUPSA Attention sub-score. However, there was a main effect of CU on NEUPSA Attention sub-scores ($F(1, 87) = 5.469$, $p=0.022$, partial $\eta 2 = 0.059$), such that HC participants had higher scores compared to BD+CU participants ($p=0.004$).

Conclusions: These findings provide preliminary evidence that the NEUPSA assesses aspects of attention (i.e., sustained attention) and executive function (i.e., risky decision making). Additionally, CU and BD may be associated with differential impacts on attention and executive function. Further research needs to be conducted on the validity of this measure and its utility in assessing neuropsychological function in clinical populations.

The Accuracy of Cannabis Users' Expectations of Drug Effects on Driving

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Background: Acute cannabis use can be associated with degraded driving performance, yet many users report that their driving ability is largely unaffected. The present study assessed the accuracy of cannabis users' driving expectations and changes in driving simulator performance following cannabis administration.

Methods: 191 cannabis users (M_{age} [SD] = 29.9 [8.3] years; 61.8% male) were assigned randomly to smoke THC or placebo cigarettes *ad libitum*. Participants completed a cannabis expectations questionnaire (e.g., would use negatively affect driving?) before study initiation, and driving simulations (which included a divided attention task) before and after cannabis administration. The primary outcome was expectation accuracy—the agreement between expectations (e.g., worse driving, no change) and impairment assessed on the simulator. Simulator impairment was based on the Composite Drive Score (CDS), a global metric comprised of standard deviation of lateral position (i.e., swerving), standard deviation of speed, divided attention correct hits, and car following. Simulator outcomes were pre-post cannabis administration change scores. The Placebo group represents no cannabis-related performance changes.

Results: Those expecting worse performance ("THC-Worse") were more likely than those expecting no effect ("THC-Same") to be classified as impaired on the simulator after cannabis administration ($p = .047$). Accuracy in predicting performance was limited; 55.6% of THC-Worse and 64.1% of THC-Same correctly anticipated their driving impairment status. Although less frequent users were more likely to expect performance declines (76.7%) than frequent users (51.9%; $p = .006$), accuracy rates (48.2–64.4%) did not differ by cannabis use (i.e., less frequent vs. frequent users, light vs. medium vs. heavy users; ps ≥ .310). When examining CDS as a continuous outcome, ANOVA indicated that THC-Same, THC-Worse, and Placebo differed ($p < .001$). Post hoc, THC-Worse demonstrated greater decrements on CDS compared to THC-Same and Placebo (ps ≤ .046).

Conclusions: Cannabis users' expectations of acute driving effects showed limited relationship to driving performance. At the group level, those expecting driving declines performed significantly worse on the simulator. However, with respect to substantial declines (i.e., impairment), expectations appear moderately accurate at best, even among the most experienced users. Cannabis legalization's public safety impact, in terms of driving impairment, remains to be fully understood. Users lack clear guidance regarding the likely effects of using different amounts of cannabis, and our findings raise concerns about users' abilities to accurately ascertain the effects of use. Further research is needed to provide robust information regarding the effects of cannabis and develop new tools for individuals to self-identify impairment.

Does the Terpene Myrcene Elicit Tetrad Effects Typical of CB1 Receptor Agonists?

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Background: While phytocannabinoids such as THC and CBD have been widely studied for pain outcomes, the other cannabis constituents, namely terpenes, have been less characterized for their therapeutic potential. Myrcene, a monoterpene found in cannabis, has been shown to have analgesic potential in preclinical pain models via engagement of the endogenous cannabinoid system. However, to what extent myrcene may elicit additional cannabinoid receptor 1 mediated effects (tetrad) in rodents remains unknown. We sought to determine whether myrcene produces outcomes typical of other CB1 receptor agonists: antiallodynia, hypolocomotion, and hypothermia in a model of chronic pain.

Methods: We used the Chronic Constriction Injury (CCI) model of neuropathic chronic pain in mice. Mechanical hypersensitivity thresholds were measured in male and female adult C57Bl/6J mice using an electronic von Frey (eVF) device 2-3 weeks after surgery and 30-minutes post-injection. Distance traveled and core body temperatures were also measured in males 4-hours post-injection in 30-minute bins. We compared myrcene (100 mg/kg, i.p.) to vehicle (corn oil) to assess drug effects on eVF, and added the positive control of cannabinoid CB1 receptor agonist CP 55,940 (1 mg/kg, i.p.) to assess drug effects on locomotion and body temperature.

Results: A two-way ANOVA comparing sex and drug (myrcene or vehicle) was conducted to analyze eVF scores. We found main effects of sex and drug ($ps < 0.01$), with males showing increased thresholds when given myrcene compared to vehicle ($p < 0.001$) and the same effect trending in females ($p = 0.0657$). A two-way repeated measures ANOVA was conducted to determine the effect of drug (myrcene, vehicle, or CP 55,940) and time on locomotion and temperature. We observed an effect of time ($p < 0.0001$) and drug ($p < 0.0001$) on locomotion; multiple comparisons revealed CP 55,940 produced hypolocomotion ($p < 0.05$) whereas myrcene did not differ from vehicle. A two-way repeated measures ANOVA showed an effect of time ($p < 0.0001$) and drug ($p < 0.0001$) on temperature with CP 55,940 significantly decreasing body temperature compared to vehicle. CP 55,940 produced hypothermia at all time points post-injection compared to myrcene or vehicle ($p < 0.001$); there were no differences between myrcene and vehicle.

Conclusions: Male mice demonstrate allodynic responses to a mechanical stimulus after CCI surgery that is reduced by myrcene. Myrcene does not elicit changes in locomotion or temperature, as compared to the CB1 agonist CP 55,940 in males.

Innovative Methods for Prenatal THC Exposure: Vaping Inhalation Chamber and Metabolite Quantification in Prairie Voles and Rats

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Introduction: The increasing prevalence of cannabis use, including among pregnant women, highlights the critical need for a deeper understanding of prenatal cannabis exposure. This study aimed to develop a standardized vaping protocol for THC administration in prairie voles (*Microtus* ochrogaster) and Sprague Dawley rats (*Rattus norvegicus*), and to investigate the distribution of THC in maternal and fetal tissues following prenatal exposure.

Methods: Using a vaping chamber method, we administered THC to pregnant prairie voles and rats. THC concentrations were measured in maternal and fetal brain tissue and plasma using LC-MS/MS (Liquid Chromatography coupled with Tandem Mass Spectrometry). In both species, THC levels were compared across groups to evaluate the impact of fetal position and sex on THC uptake.

Results: The study found that THC successfully crossed the placental barrier in both species, resulting in significantly higher concentrations of THC in the fetal brain within the dosed groups compared to the vehicle. Maternal brain THC concentrations were significantly higher than fetal concentrations in prairie voles. Strong positive correlations were observed between plasma and brain THC concentrations in both maternal and virgin adult prairie voles. No significant effects of fetal position or sex on THC levels were found. Interspecies comparison revealed higher THC concentrations in rat fetal brain tissue compared to prairie voles.

Conclusions: This study establishes a translational model for investigating prenatal cannabis exposure using a vaping administration method. The findings confirm placental transfer of THC and reveal species-specific patterns of THC distribution. The standardized protocol and results provide a foundation for future research into the developmental consequences of prenatal cannabis exposure and offer crucial insights for informing public health policies and clinical practices in response to the global increase in cannabis use.

Recent Cannabis Use Moderates the Association Between Methamphetamine Use and Increased Markers of Inflammatory and Immune Processes

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Background: Cannabis is reported to contain compounds that have anti-inflammatory effects, and this is the basis for increased interest in them as potential medicines. We were curious whether, in a naturalistic setting, the use of cannabis might modify the inflammatory cascades produced by HIV and methamphetamine use disorder. To explore these associations, we examined profiles of plasma markers of inflammatory and immune functions in groups with and without HIV infection and methamphetamine use disorder, and we examined differential associations on the basis of reported cannabis use in the past month.

Methods: We examined data from HIV-seropositive adults on suppressive antiretroviral therapy (PWH, n=86) and HIV-seronegative adults (PWoH, n=148) with lifetime histories of METH use, cannabis use, or both. Data were collected using standardized neuromedical, psychiatric, and medical history interviews. Soluble levels of immune and endothelial activation (i.e., chemokines CXCL10/IP-10 and CCL2/MCP-1, cellular adhesion molecules ICAM-1 and VCAM-1, and uPAR) were measured using electrochemical luminescence immunoassays. We used multivariable linear regression models to examine associations between HIV status (PWoH/PWH), lifetime DSM 5 methamphetamine use disorder (MUD-/MUD+), past month cannabis use (C-/C+), and markers of inflammatory and immune processes. We adjusted for potential variability in test kits over the study years by applying a median absolute deviance correction to plasma marker levels within analysis plate measurements.

Results: Participants were, on average, 42.0±13.6 years of age, 76% male, 52.8% White, and educated 13.8±2.5 years. PWH displayed significantly higher levels of VCAM-1 (B=0.34) and IP-10 (B=0.55). MUD+ was independently associated with higher levels of VCAM-1 (B=0.28) and MCP-1 (B=0.37). Past-month cannabis use was independently associated with lower levels of IP-10 (B=-0.29). We found no significant interactions between HIV status and MUD or past-month cannabis use. However, interactions between past-month cannabis and MUD were significant in models of VCAM-1 and MCP-1, with MUD+ participants with past-month cannabis use displaying lower levels than those without past-month cannabis use.

Conclusions: The results suggest that cannabis use may be associated with lower levels of some biomarkers such as IP-10, independent of methamphetamine history. In other cases (VCAM-1 and MCP-1) an attenuation effect of recent cannabis use was found for methamphetamine users, in particular. Deleterious impacts of HIV status and MUD were found to be only additive in nature. The results, if confirmed, do suggest that recent cannabis use may ameliorate pathogenesis associated with inflammatory cascades, both in people with and without HIV.

Cannabis Use, Bipolar Disorder, and Exploratory Behavior in the Human Behavioral Pattern Monitor: A Preliminary Analysis

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Introduction: Cannabis use (CU) is far more common among individuals with bipolar disorder (BD), and as a result has become an increasingly important area of research. The human behavioral pattern monitor (hBPM) is a cross-species translatable open field test designed to measure exploratory behavior in clinical populations. Our previous findings have shown that the hBPM can quantify the increased activity and energy that is characteristic of BD and can provide a more nuanced understanding of behavioral endophenotypes associated with psychiatric disorders compared to traditional methods. This preliminary study aimed to compare how patterns of exploratory behavior are associated with CU and BD.

Methods: We recruited 54 participants, including participants with BD and healthy comparison participants (HC), who either regularly use cannabis (+CU) or do not use cannabis. The hBPM paradigm consisted of a single 15-minute session during which participant behavior was monitored via a hidden video camera. hBPM outcome variables included total number of object interactions, spatial *d* score (the spatial organization of their locomotor pathway represented across 1 to 2 dimensions), total travelled distance (represented by movement increments plotted by the length of the room), and counts (a participant's total activity represented by the total number of discrete instances of movement). We employed Kruskal-Wallis tests and a two-way ANOVA to test for differences between our four comparison groups (HC+CU n=18, BD+CU n=11, BD n=8, HC n=17).

Results: There was no significant interaction between BD and CU on counts ($F(1, 50) = 2.6$, $p=0.113$, partial $\eta 2 = 0.049$). There was no difference between HC and BD or HC and HC+CU in counts. However there was an observed trend between the BD and BD+CU group, where the BD+CU group had less overall activity compared to the BD group ($F(1, 50) = 3.826$, $p=0.056$, partial $\eta 2 = 0.071$). No effects were seen for spatial d, travelled distance and total object interactions between any of the groups.

Conclusions: CU in people with BD was associated with lower activity levels compared to non-CU people with BD, consistent with our previous findings that cannabis use is associated with better cognitive functioning in this cohort. These findings provide insight into the potential effects of CU on people with BD, where CU may be associated with differential behavioral patterns compared to HC participants. Future analyses will include other hBPM and CU variables, as well as a cross-species comparison of data from our anaimal open-field experiments.

Hydrogenation of Phytocannabinoids

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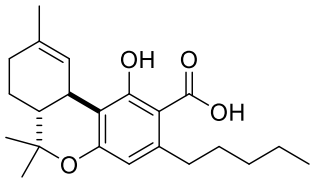
Background: The phytocannabinoids from cannabis have been shown to possess a myriad of therapeutically important biological activities. The isolated compounds themselves may also be viewed as reactive species that can serve starting materials for other structural derivatives through the use of different chemical transformations. These analog compounds maintain much of the molecular features of the phytocannabinoid starting materials while introducing minor structural modifications which can enhance their biological activity while maintaining their inherent safety of in humans and animals.

Methods: Recently, hydrogenation of THC is being used to produce hexahydrocannabinol (HHC), a non-natural synthetic derivative that has recently received a lot of attention. Applying hydrogenation broadly to phytocannabinoid starting materials provides access to library of hydrogenated derivatives that includes hexahydrocannabinolic acid (HHCA) and tetrahydrocannabidiol (THCBD). Hydrogenation of the unsaturated groups of the phytocannabinoids converts them into their fully saturated derivatives.

Results: We have explored the impact that hydrogenation has on the biological activity of these compounds in antibacterial assays.

Conclusions: The use of these derivatives in potential therapeutic applications will be presented.



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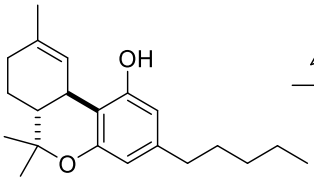

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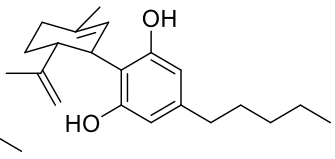

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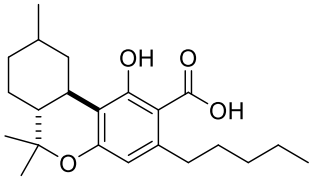
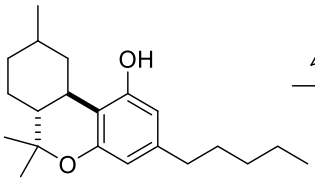
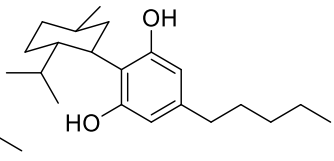


HHCA



HHC



THCBD

Effects of Psychotomimetic Doses of Δ9-THC on EEG Measures of Excitatory-Inhibitory Balance and its Relationship to Neural Noise

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Background: There is a balance between the excitatory and inhibitory (E/I) inputs driving pyramidal cell activity that is essential for brain function and is altered in various neuropsychiatric disorders[1–3]. The aperiodic component of EEG signals has a $1/f^{\alpha}$ ($\alpha>0$) exponential relationship between frequency and power spectral density (PSD) and the exponent α has been shown to be inversely correlated with E/I ratio[4]. The activation of cannabinoid type I receptors (CB1R) is known to disinhibit pyramidal cell activity. We hypothesized that Δ9-THC, the main active constituent of cannabis, will disinhibit neural circuits and lead to increased E/I ratio

Methods: In this double-blind, placebo-controlled, randomized, within-subject study, 25 human participants received intravenous Δ9-THC (0.015 mg/kg, 0.03 mg/kg, and placebo) on three test days while they completed an EEG auditory oddball task[7]. Behavioral effects were captured with Positive and Negative Syndrome Scale (PANSS). Aperiodic exponents and Lempel-Ziv complexity (LZC) of the pre-stimulus period[9,8] were used as proxy measures of brain circuit disinhibition. The effect of drug condition on exponents and LZC, as well as their relationship with PANSS scores, was assessed using generalized estimating equations (GEE). p-values were adjusted using Holm-Bonferroni (HB) method.

Results: The statistical analyses showed a significant effect of drug condition on aperiodic exponent (Wald X^2 =75.729, $p < 0.001$). Pairwise comparisons revealed significantly lower exponent values in both active conditions compared to placebo (both $p_{Adj} < 0.001$). No differences between high and low doses of Δ9-THC were observed ($p_{Adj} > 0.05$). The GEE longitudinal regression showed a significant negative relationship between aperiodic exponent and positive (β = -0.288, Wald X^2 = 5.978, p_{Adj} = 0.014) and total (β = -0.196, Wald X^2 = 3.870, p_{Adj} = 0.049) log transformed PANSS scores. Furthermore, the analyses showed a negative relationship between exponents and LZC (β = -0.367, Wald X^2 = 12.458, $p_{Adj} < 0.001$).

Conclusions: At psychotomimetic doses, Δ9-THC reduced the aperiodic exponent during the attentional period of an oddball task. Furthermore, there was a negative relationship between exponents and positive and total PANSS scores. In view of the relationship between aperiodic exponent and E/I ratio, these results suggest that THC induces a state of disinhibition related to the drug's psychoactive effects. The inverse relationship between exponents and LZC suggests that LZC may be sensitive to the changes in E/I ratios.

Impact of Cannabinoids on Interferon-Stimulated Gene Expression and HIV Infection in Macrophages

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Introduction: Chronic inflammation plays a key role in HIV progression, with interferon-1 (IFN-1) signaling contributing to chronic activation and immune exhaustion. Blocking IFN-1 receptor boosts antiviral responses in HIV-infected humanized mice. Cannabis, widely used in the U.S. especially among people with HIV, contains cannabidiol (CBD) and Delta-9-Tetrahydrocannabinol (THC), which have anticonvulsive, analgesic, and anti-inflammatory effects. Consequently, CBD and THC have emerged as potential candidates for alleviating immune exhaustion and improving the clinical management of chronic inflammation in HIV infection.

Methods: The monocytic cells THP-1 was exposed to CBD, THC, or a vehicle, with and without stimulation using 2'3'-cGAMP or LPS. High-throughput RNA-Seq analysis was conducted to explore the differential gene expression in these cells. Validation of differentially regulated genes was carried out in THP-1 cells using quantitative real-time PCR. Western blot analysis was performed on THP-1 cells treated with either vehicle or CBD to investigate changes in the expression of autophagy markers LC3B and p62 following 2'3'-cGAMP stimulation. Primary cells were treated with cannabinoids, followed by short-term and long-term HIV infection, with quantification of HIV RNA levels and type I IFN genes using RT-PCR.

Results: Transcriptomic analysis and confirmatory real-time PCR revealed universal downregulation of type I interferon-associated genes in CBD- and THC-treated THP-1 cells compared to vehicle-treated cells following 2'3-cGAMP and LPS stimulation. Interestingly, increased levels of autophagy, were observed in CBD- and THC-treated cells as compared to vehicle control. In human primary macrophages, we observed differential impact of CBD and THC on HIV infection. We found that in primary macrophages, CBD decreased ISG expression upon HIV infection, increasing HIV RNA levels initially. However, CBD decreased long term viral spread in treated macrophages. THC similarly downregulated ISGs, but also notably decreased CCR5 expression, leading to reduced viral RNA level during both acute and long-term R5 tropic HIV infection.

Conclusions: CBD and THC regulate a diverse array of gene expressions related to inflammation, energy homeostasis, and metabolism in monocytes and microglia cells. These cannabinoids downregulate IFN-1 response genes and induce an increase in autophagy-related genes after stimulation. In the context of HIV infection, CBD decreases the expression of Type 1 IFN genes, leading to increased HIV RNA expression during acute infection; while THC, potentially through reduced CCR5 coreceptor expression, decreases HIV RNA level and ISG expression. Importantly, long-term culture with CBD and THC in infected primary macrophages reduces HIV viral spread, suggesting potential roles of cannabinoids in inhibiting HIV replication.

Delta-9-Tetrahydrocannabinol Produces Consistent Physiological and Motivational Effects in HIV-1 Transgenic Rats Relative to Their Controls

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Background: People with HIV (PWH) use cannabis at higher rates than the general population and clinical data cites that it may alleviate HIV-relevant symptoms, including HIV-associated neurocognitive impairment (NCI). Few experimental studies on the physiological and cognitive effects of cannabis in PWH exist, however. Such studies are needed but have clinical confounds difficult to control for (e.g., frequency of use, age), whereas testing in animal models enables controlling for these confounds. Delta-9-tetrahydrocannabinol (THC) is the primary psychoactive component of cannabis and has anti-inflammatory and neuroprotective properties that may play a significant role in cannabis-induced symptom alleviation in PWH. Here, the physiological effects of acute THC and motivational effects of acute and chronic THC were tested in HIV-1 transgenic rat model of neuroHIV.

Methods: Experiment 1: Adult female and male HIV-1tg (n=46) rats and their controls (wildtypes; WT and F344 n=87) were tested for acute THC-induced (0, 0.3, 3 mg/kg) physiological effects using the cannabinoid tetrad assay: 1) tail immersion test (nociception), 2) rectal temperature, 3) Behavioral Pattern Monitor (locomotor and exploratory behavior). Experiment 2: Adult female and male HIV-1Tg (n=58) rats and controls (n=84) restricted to 85% of free-feeding weight were tested in the Progressive Ratio Breakpoint Task (PRBT) to measure effortful motivation. Animals were tested at baseline, then again following both acute, and chronic (16 days) THC-exposure (same doses as Exp. 1). The main outcome variable was the breakpoint (last trial wherein an animal stops responding for reward).

Results: Experiment 1: High dose THC dose-dependently reduced nociception [$F(2,115)=22.879, p<0.001$], produced hypothermia [$F(2,115)=24.672, p<0.001$], and decreased locomotor [$F(2,115)=4.550, p=0.013$] and exploratory behavior [$F(2,115)=10.527, p<0.001$], irrespective of genotype. Some effects were sex-dependent. Experiment 2: HIV-1Tg rats and their WT littermates exhibited reduced motivation at baseline [genotype: $F(2,120)=8.898, p<0.001$], during acute THC [genotype: [$F(2,123)=12.105, p<0.001$], and during chronic THC [genotype: [$F(1,122)=3.468, p=0.065$] testing timepoints when compared to F344 control rats. Acute high-dose THC tended to decrease breakpoints across sex and gene [drug: [$F(2,123)=2.958, p=0.056$], but this effect was no longer observed following chronic THC administration.

Conclusions: High-dose THC produced the cannabinoid tetrad (nociception. hypothermia, and hypomotility) in a manner that was not influenced by the HIV-1 transgene. In the PRBT, HIV-1Tg rats exhibited reduced breakpoints relative to F344 rats across all time points, suggesting impaired motivation. Consistent with the tetrad, acute high-dose THC reduced motivation regardless of genetic differences. Thus, acute THC produced consistent physiological and motivational effects in HIV-1Tg rat model of neuroHIV as their controls.

State of Medical Cannabis in California

Sherry Yafai, Goldstein Bonnie

The Releaf Institute and Canna Centers

Background: Medical cannabis in California has come a long way since it originally was medically legalized in 1996. In 2018, with the passage of adult-use laws, the landscape has evolved significantly, and questions have been raised about the role and practice of medical cannabis within the clinical setting. To more thoroughly understand this, we have secured a grant from the Department of Cannabis Control DCC to evaluate the state of medical cannabis through the lens of four independent cannabis physicians and their patients.

Methods: A survey was created to evaluate the following aspects of a medical cannabis patient: 1) age, gender, caregiver involvement; 2) specific types and amounts of cannabis used (including hemp) and associated costs; 3) duration of medical cannabis use and approval Length of medical usage/approval; 4) patient-reported improvements, side effects, and ER visits as a result of medical cannabis.

Results: To date, we have accumulated over 500 active patient surveys that provide insights into the health profiles of medically supervised cannabis patients. Patients range in age from infants and teenagers, whose care is always managed by their parents/guardians, to seniors, some of whom have dementia or mild cognitive impairment and are supported by caregivers. Diagnoses ranged from Autism Spectrum Disorder, cerebral palsy, cancer, dementia, Parkinson's, to chronic and neuropathic pain management. Notably, there have been no emergency room visits reported as a direct result of cannabis use among our patients.

Conclusions: We are in the midst of the data analysis at this time and more detailed findings will be presented at the upcoming UCSD conference. Preliminary results indicate the demographic profile of medical cannabis patients is broader than that suggested by existing studies, which tend to depict cannabis users as males between ages 20 to 40. Our findings reveal that patients who seek medical care include both pediatric, and senior populations. Patients under physician-guided care tend experience better short- and long-term outcomes, reduce their reliance on other medications and avoid emergency room visits. We observed little to no side effects from physician-managed cannabis use. In contrast, individuals who self-administer cannabis appear more likely to have side effects necessitating ER visits. Overall, physician-supervised cannabis use overall has a positive impact on patient outcomes, even amidst the change in legal and policy landscapes that have increased access.